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Clinical Studies

The Coronary Profile

An Approach to the Preclinical Diagnosis of Coronary Artery Disease

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THE HIGH incidence of coronary atherosclerosis has made it mandatory that methods are devised for detecting, in its early and preclinical phase, this incapacitating and often fatal disorder.[1] It has become obvious in the recent past that our present diagnostic methods are both gross and inadequate.[2] Not only is it true that no single diagnostic element is sufficient to draw any definite conclusion concerning the status of the coronary arteries, but all too often a patient has been subjected to a gamut of medical and laboratory tests, with no defects being demonstrated, only to succumb shortly thereafter to coronary artery disease.

While it is recognized that some of the most basic mechanisms of the etiology and pathogenesis of coronary artery disease are unknown,[3] this does not preclude the possibility of establishing by association a reliable diagnostic system with community-wide applicability for the preclinical detection of this disorder.

A definite need exists, therefore, for a diagnostic approach which will reliably identify individuals predisposed to coronary artery disease before clinical symptoms are manifest. Such a diagnostic approach should lend itself to widespread application without recourse to complicated equipment and costly procedures.

The Framingham,[4] Albany[5] and Los Angeles[6] studies have approached this problem on a widespread, statistical basis in an attempt to ascertain what correlative conclusion could be formulated between diagnostic examinations and coronary heart disease.

THE CORONARY PROFILE

The coronary profile is an approach to the problem of detecting atherosclerosis in its incipient stages. This term is not unique with the authors, as it was introduced with a slightly different connotation in the work of Gertler, Garn, and White[7] in 1951. The nomenclature is desirable, however, as it expresses the multidimensional approach to the diagnostic problems of coronary artery disease.

As noted above, this approach results from recognition of the fact that no one diagnostic method, alone, contributes enough information

to draw definite conclusions about the status of the coronary arteries.[8] For example, the blood lipids[9,10] by themselves are not adequate diagnostic tools, nor is the electrocardiogram or the x-ray examination.

An attempt has been made with the coronary profile, however, to combine chemical and physical tests, x-rays, and personal history data into a semiquantitative rating system, which will reliably identify persons predisposed to coronary artery disease. It is mandatory to emphasize that this approach embodies a relative rather than absolute numerical evaluation of a patient's cardiovascular system. It appears, however, from the authors' experience, that when these tests are placed together in a grading system, the results represent a reliable indication of an individual's cardiovascular status.

The coronary profile, as demonstrated in Figure 1, assigns to the lipid chemistries of an individual 45 per cent of the total profile. The lipid chemistries, with equal ratings,[11] are defined in this instance as the measurement of alpha and beta lipoproteins by electrophoresis,[12] the athero-index of Barr,[13] and the determination of cholesterol, using the modified Zak method.[14] Twenty per cent of the profile is classified in the physical examination, 5 per cent being allotted to the blood pressure, another 5 per cent to peripheral vascular change, and 10 per cent to the eye-ground changes. Electrocardiographic studies account for 20 per cent of the coronary profile, with stress electrocardiograms, comprised of a modified Master's test,[15] composing the bulk of the percentile ranking.

Ten per cent of the profile is then given over to x-ray examination of the heart and aorta. Aortic abnormality is distinguished, using oblique films of the chest, noting the presence of widening, tortuosity or calcification. Five per cent of the profile involves arteriosclerotic cardiac symptoms, which may be past history of coronary artery disease with premonitory symptoms such as dyspnea, vertigo, chest pain, weakness, diaphoresis, or true angina.

To compile the profile, standards (Table I) have been set up in which the subject loses a given number of percentile points in direct relationship to demonstrated abnormalities. The more abnormal the patient's findings, the lower his grade. It is important to re-emphasize that evaluating these patients is not an attempt to quantitate their abnormalities, which obviously cannot be done by inference, but merely to place them into a semiquantitative profile rating zone. Each subject is assigned to a rating zone designated as "red," "yellow" or "green," depending upon his total grade (Fig. 2).

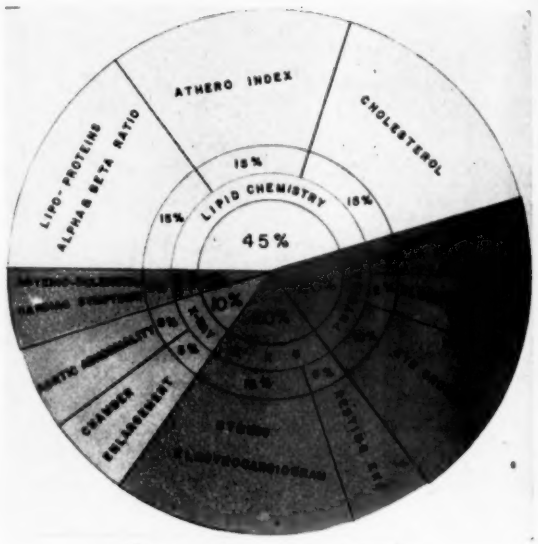

Fig. 1. The coronary profile.

The *red zone* (0 to 74 per cent) is interpreted as poor cardiovascular status, with the possibility of pathogenic cardiovascular changes appearing clinically in the near future. The *yellow zone* (75 to 84 per cent) indicates that there is concern about the status of the coronary arteries, while the *green zone* (85 to 100 per cent) means that the investigators feel that the integrity of the cardiovascular status is within normal limits.

Study Method

The initial phases of this work were performed at the Aero-Medical Laboratories, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio. Latter phases have been accomplished at the laboratory of the senior investigator in Dayton, Ohio.

One hundred forty-nine male Air Force personnel and 14 civilian personnel, between the ages of 20 and 70 years, were selected as study subjects. The 149 military personnel were

TABLE I

Grading System of the Coronary Profile

	Category	Normal rating %	Values	True rating %
Lipid chemistry	Lipoproteins ratio of beta lipoproteins	15	Less than 85%	15
			87–87%	12
			87–90%	10
			90–93%	5
			93–100%	0
	Athero-index Q-quotient	15	Above 1.3	15
			1.0–1.3	12
			0.98–1.0	10
			0.95–0.98	5
			Below 0.95	0
	Cholesterol	15	Less than 180 mg%	15
			180–220 mg%	12
			220–250 mg%	10
			250–275 mg%	5
			Above 275 mg%	0
Physical	Peripheral vascular aging—atherosclerotic type	5	Graded as either 5% or 0% according to vascular changes	
	Blood pressure	5	Graded as either 5% or 0% according to Master's standards	
	Eyegrounds	10	Eyegrounds normal	10%
			Increase in number of branches across disc margin	5%
			Plaque formation, Bedell's sign	0%
			%	
Electrocardiogram	Resting	5	5	Graded as either 5% or 0% if coronary changes present
	Stress ECG	15	15	Normal
			10	ST depression of 2 mm or more in any precordial or limb lead
			5	Inverted T or flat T, after being upright in any lead
			0	Combination of above or appearance of an arrhythmia
X-ray	Aortic abnormality	5	5	Graded as either 5% or 0% if aortic changes of dilatation or calcification are present
	Chamber enlargement	5	5	Graded as either 5% or 0% if chamber enlargement is present
History	Arteriosclerotic symptoms present	5	5	Graded as either 5% or 0% if any definite arteriosclerotic symptoms

divided between enlisted men and officers on a 1:3 ratio. All had passed routine Air Force medical examinations, while most had qualified for flying status. An additional 32 persons who had had previous coronary abnormalities of a clinical nature were also studied to aid in the selection of appropriate rating values. The term "coronary abnormalities" is used through-

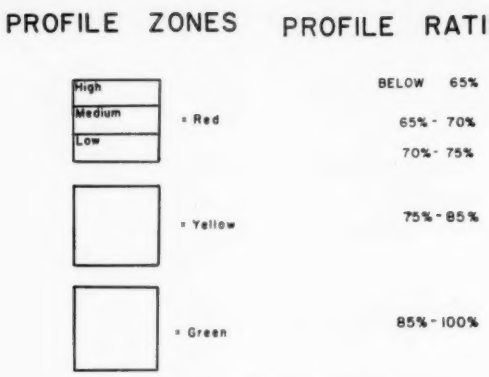

Fig. 2. Rating zones of coronary profile.

out this paper, following the classification of arteriosclerotic heart disease proposed by the New York Heart Association.[16] The five distinct categories of coronary artery disease listed herein comprised the criteria for classifying a patient as having coronary abnormalities:

(1) Myocardial infarction with historical and laboratory confirmation.

(2) Coronary occlusion, causing sudden death.

(3) Angina pectoris of an unequivocal and classic nature.

(4) ECG evidence of possible myocardial infarction such as deep Q_3 or Q in aVF, with variable T wave changes, or deep Q, inverted T in V_{4-6} and absent R over the right precordium. These may occur in patients without history of heart disease.

(5) Myocardial fibrosis as evidenced by the clinical course of the patient or by necropsy findings as due to coronary atherosclerosis.

As each subject completed his coronary profile, a rating between zero and 100 was assigned to him. At the completion of profiles on the first 50 and first 100 subjects, the rating values were reviewed. Slight changes were made in the proportion of the total rating assigned to test elements of the profile. Adjustments were then made in the rating values resulting from specific test results. Originally, the lipids were given a 60 per cent rating in the profile, with the lipoproteins and cholesterol having a 2:1 ratio over the athero-index. Our experience with retrograde analysis of patients modified this to the lipids' final rating value of 45 per cent.

Very few subjects were shifted to different zones by these adjustments. Beyond the first 100 subjects, the numerical evaluations of the segments of the profile were not changed. All ratings shown in the data are based on the final rating method selected by the investigators.

Subsequent to the coronary profile rating, subjects were followed for varying time periods of up to four years to determine whether coronary abnormalities of a clinical nature developed. None of the test subjects was known to be under medical treatment relative to his coronary artery status during the follow-up period, except those subjects who sought medical care after developing clinical coronary abnormalities. There were, however, 31 addi-

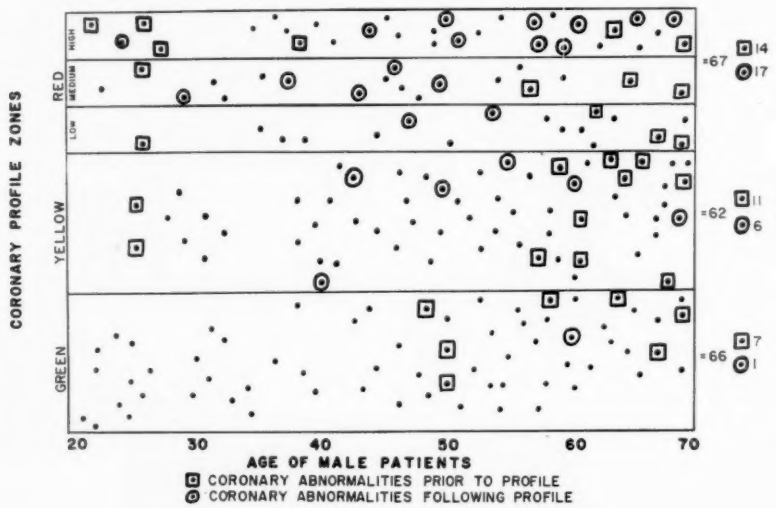

Fig. 3. Scattergram of coronary profile zones.

tional persons tested who were found to be in the red zone and who sought therapy.[17] These were not followed up and do not appear in the data of the study.

Findings of Coronary Profile

The scattergram in Figure 3 shows the coronary profile ratings of both the 163 test subjects and also of the 32 persons known to have had clinical coronary abnormalities prior to the study.

Of the latter group, 14 had coronary profile ratings in the red zone, 11 in the yellow zone, and 7 in the green zone. Those in the green zone, however, were all on various therapeutic regimens; i.e., dietary fat restriction, drug therapy, anticoagulants, fat blocking agents, etc.

Of the 163 test subjects, 53 had coronary profile ratings in the red zone, 51 in the yellow zone, and 59 in the green zone. Subsequent to the coronary profile ratings, 17 subjects in the red zone developed clinical symptoms of coronary artery disease. This occurred in 6 subjects in the yellow zone and one subject in the green zone.

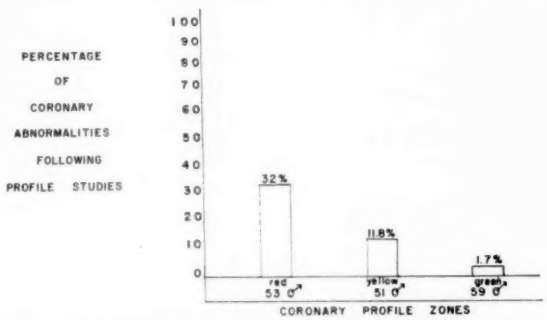

Fig. 4. Summary of coronary profile studies of 163 male patients.

When translated into percentages (Fig. 4), 32 per cent of subjects in the red zone, 11.8 per cent of those in the yellow zone, and 1.7 per cent of those in the green zone developed clinical symptoms of coronary artery disease subsequent to their coronary profile rating.

Statistical Evaluation of the Coronary Profile

An attempt was made to determine the statistical significance of the differences observed through the application of the chi-square test.

TABLE II

Predictive Value of Coronary Profile Rating at Different Age Levels

Age	Red zone		Yellow, green zones	
	Total subjects	Coronary abnormalities	Total subjects	Coronary abnormalities
20–50	30	9 (30%)	57	3 (5%)
51–70	23	8 (35%)	53	4 (8%)

The observations in the yellow and green zones were combined and Yates correction was applied. It was found that differences as great as or greater than those observed between the experience of the red group compared to that of the yellow and green groups combined would be expected as a result of sampling variation less than one time in a thousand. It might therefore be concluded as highly probable that the coronary profile system is a reliable method of identifying individuals who may be in rather imminent danger of developing clinical symptoms of coronary artery disease.

Since the risk of developing clinical symptoms of coronary artery disease varies considerably with age, an attempt was also made to determine whether the coronary profile ratings had similar predictive values at different age levels. As outlined in Table II, of 87 subjects in the age range 20 to 50 years 30 were placed in the red zone, while 57 had ratings in the yellow or green zones. Nine of the red group (30 per cent) and only three of the yellow or green groups (5 per cent) subsequently developed clinical atherosclerotic symptoms.

Of 76 subjects in the age range 51 to 70 years, 23 were in the red zone and 53 were in the yellow or green zones. Eight of the red group (35 per cent) and only four of the other groups (8 per cent) subsequently developed clinical atherosclerotic symptoms. The similarity of experience in these two broad age groups would seem to suggest that the coronary profile system has approximately similar value in predictability at different age levels.

An attempt also was made to further refine the

TABLE III

Age Distribution in the Three Coronary Profile Rating Zones

Age	Coronary profile rating zones		
	Red	Yellow	Green
20–30	3	3	13
31–40	11	8	10
41–50	16	14	9
51–60	13	15	18
61–70	10	11	9
Total	53	51	59

TABLE IV

Age Distribution in Red and Combined Yellow and Green Coronary Profile Rating Zones

Age	Red zone (%)	Yellow, green zones (%)
20–30	5.7	14.5
31–40	20.7	16.4
41–50	30.2	20.9
51–60	24.5	30.0
61–70	18.9	18.2
Total	100.0	100.0

predictability value of the coronary profile system by dividing the red zone into three subzones. The high red zone contained persons with coronary profile ratings of less than 65 per cent. The medium red zone range was 65 to 69 per cent. The low red zone range was 70 to 74 per cent.

Twenty-five test subjects fell within the high red zone, and ten of these subsequently developed clinical atherosclerotic symptoms. Because of the few subjects in the low red zone, these were combined with the medium red zone to yield a total of 28 test subjects, seven of whom developed similar symptoms.

The chi-square test was applied to these values to determine the probability that the observed differences might have resulted from sampling variation. It was found that differences as great as or greater than those observed in the post-rating development of clinical coronary abnormalities of these groups could be expected to result from sampling variation more than 20 times in 100. It was therefore concluded that proof of any value which such a division of the red zone may have in more reliably predicting coronary abnormalities must await further study.

Discussion

There are, indeed, many qualifications to this

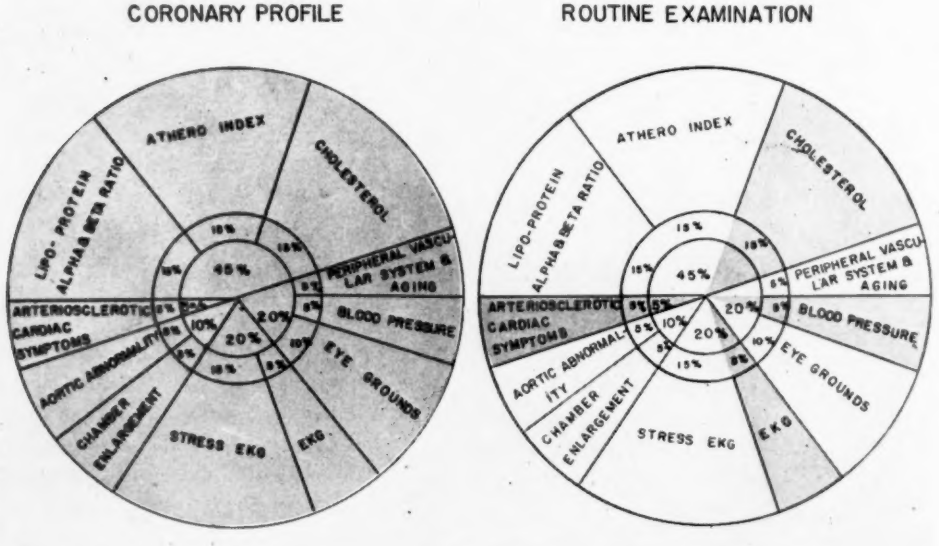

Fig. 5. Comparison of coronary profile system and routine physical laboratory examinations.

study which limit the generalization which might be made from it. First, it should be noted that the test subjects do not represent a random sample of the general population. All of the test subjects were males, and 91 per cent of these were military personnel. This, of necessity, imposes certain limitations, as the military life is not strictly comparable to civilian life.

A second qualification of this study concerns the age distribution of test subjects in the different zones. As can be seen in Table III, the green zone had a greater number of younger men than did either the red or yellow zones.

Since risk of clinical coronary atherosclerosis increases with age,[18] the effect of this age distribution would be to favor the green group, thereby tending to overstate the value of the coronary profile system. This has been partially dealt with in the preceding analysis by combining the green and yellow groups. This results in a percentage age distribution as shown in Table IV.

A third qualification of the study relates to the varying lengths of time test subjects were followed after being rated by the coronary profile system. Although no data are presented here, a comparison was made of the lengths of the follow-up periods of test subjects in each rating zone. It was found that within the overall limit of four years, relatively similar periods of time were involved for each group. It may be of interest to note that 15 of the 17 red zone subjects who later developed atherosclerotic signs and symptoms of a clinical nature did so within 18 months after their coronary profile rating. It should, perhaps, also be noted that the one test subject in the green zone who subsequently developed clinical atherosclerotic symptoms, in an 18-month period gained 23 lb, was placed in a job requiring a constant 14-hour-work day, stopped all exercising and increased his daily tobacco consumption to two and one-half packs per day between the time of his coronary profile rating and the onset of clinical manifestations of coronary artery disease. It is very strongly suspected that a coronary profile rating done on this subject just prior to the development of clinical symptoms would have resulted in placing him in the red zone.

The coronary profile system is compared in Figure 5 to the physical and laboratory examinations usually included in a routine diagnostic evaluation. The shaded areas representing the tests performed in the routine examination total only 30 per cent of the coronary profile. This discrepancy, the authors feel, strongly contributes to the inadequacy of routine diagnostic surveys of the cardiovascular status.

Summary

The coronary profile approach to the preclinical diagnosis of coronary artery disease is presented, with results of a pilot project which suggest its reliability in identifying individuals imminently in danger of developing clinical coronary abnormalities. The coronary profile rating includes blood lipid chemistries (45 per cent), physical examination (20 per cent), resting and stress ECG (20 per cent), x-ray findings (10 per cent), and history (5 per cent). Clinical abnormalities suggestive of coronary artery disease were more common in those subjects with a poor profile rating (red zone) than in those with a higher rating (yellow and green zones). The potential values of this approach would appear to justify further investigation of its reliability and its possible modification into a simplified detection method with community-wide applicability.

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Transaminase Activity in Coronary Heart Disease

Determinations of Serum Lactic Dehydrogenase, Glutamic Oxalacetic Transaminase, and Glutamic Pyruvic Transaminase Activity*

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DETERMINATION of certain serum enzymes, most notably lactic dehydrogenase (LDH), glutamic oxalacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT), has been introduced as a laboratory aid in the differential diagnosis of myocardial infarction. The rationale for testing the activity of these enzymes is based on the observation that serum levels were substantially increased in the presence of acute myocardial infarction.[1] Presumably with myocardial necrosis the disrupted cells release the enzymes, which pass into the circulation where the resultant elevation can be measured.[2,3]

The present study was designed to compare the maximum serum activity of LDH, GOT, and GPT in 40 patients with symptomatic coronary heart disease.

MATERIALS AND METHOD

Venous blood was drawn for the analysis of lactic dehydrogenase and glutamic oxalacetic transaminase as previously described.[4]

Glutamic pyruvic transaminase (GPT) was assayed by the method of LaDue.[5] All assays were run at 25°C using a Beckman DU Spectrophotometer. One unit of GPT activity is equal to a decrease in optical density of 0.001 per ml of serum per minute at 23°C. Forty-one adults, 10 males and 31 females, ranging in age from 17 to 49 years, served as controls for the LDH; 28 adults, 3 males and 25 females, 8 to 47 years of age, served as controls for serum GOT activity; and 34 adults, 6 males and 28 females, ranging in age from 17 to 49 years of age, were used as controls for serum GPT activity.

RESULTS

Results of serum LDH determinations are plotted graphically in Figure 1. Each dot represents the highest activity in a single patient or control without regard to time. The serum LDH activity of 41 apparently healthy hospital personnel ranged from 50 to 131 LDH units per 0.01 ml, with a mean of 78.

Lactic Dehydrogenase Activity: The LDH activity was increased in all 20 patients who had electrocardiograms diagnostic of recent myocardial infarction (Fig. 1, group A). The increased activity ranged from 156 to 1050 units. Nine patients were studied who had electrocardiograms consistent with acute coronary insufficiency (Fig. 1, group B). Three of these patients exhibited values within the normal, and the remaining six had elevated levels, with a range from 145 to 280 units. Six patients were studied who had the clinical picture of angina pectoris

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with normal electrocardiograms (Fig. 1, group C). Four of these patients had normal levels, and two had elevated levels, with peak activities of 180 and 280 units. Twenty-eight patients whose final clinical diagnosis was recent myocardial infarction without regard to electrocardiographic findings were selected from groups A, B, and C and assigned to a fourth group, D (see Fig. 1). These 28 patients all had elevated LDH levels ranging from 145 to 1050 units.

Glutamic Oxalacetic Transaminase Activity: Results of GOT determinations are plotted graphically in Figure 2. Each dot represents the highest activity in a single patient or control without regard to time. The serum GOT activity of 28 presumably healthy controls ranged from 7 to 31 units per ml, with a mean of 16.

The GOT activity was increased in 18 of the 20 patients who had electrocardiograms consistent with acute myocardial infarction (Fig. 2, group A). The activity ranged from 35 to 340 units. In the two cases with normal values the serum was not drawn until four and six days, respectively, after the onset of pain. Nine patients had electrocardiographic evidence of acute coronary insufficiency (Fig. 2, group B). Four of these showed GOT levels within normal limits, and five had elevated levels, with a range from 35 to 110 units. In the six patients with a typical anginal syndrome, three showed levels within the normal range (Fig. 2, group C). Three presented elevations with peak levels of 45, 60, and 85 units. Group D (Fig. 2) comprises the 28 patients with a clinical diagnosis of myocardial infarction selected in the same fashion as above. Twenty-four of these patients presented elevated levels, with a range from 35 to 345 units.

Glutamic Pyruvic Transaminase Activity: The results of serum GPT determinations are plotted graphically in Figure 3. Each dot represents the highest activity in a single patient or control without regard to time. The serum GPT in 34 normal controls varied between 3 and 23 units, with a mean of 9 units.

Serum GPT activity was determined in 18 of the 20 patients with electrocardiographic evidence of acute myocardial infarction. In seven of these cases the enzyme activity was increased, with a range from 25 to 75 units (Fig. 3, group A). Nine patients with electrocardiographic evidence of acute coronary insufficiency (Fig. 3, group B) were studied for GPT activity, and of these, seven were in the normal range. Two were elevated, showing peak activities of 60 and 70 units. Five cases of angina pectoris were studied, and of these four were in the normal

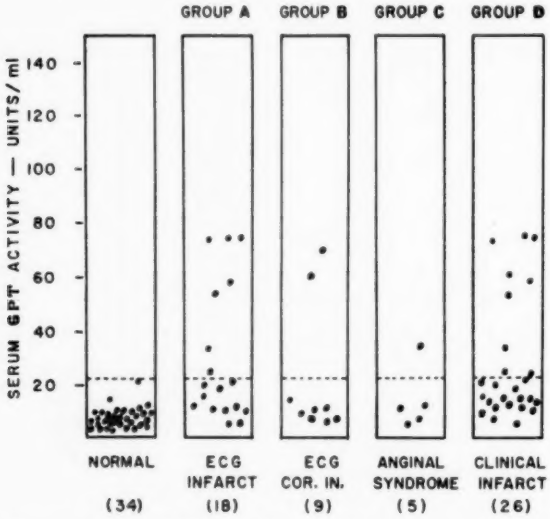

Fig. 1. Serum LDH activities in 40 patients with coronary disease. Each dot represents the highest activity observed in a single patient. Dotted line is the upper limit of normal. Figures in parentheses refer to the total number of patients in a particular category as described in the text.

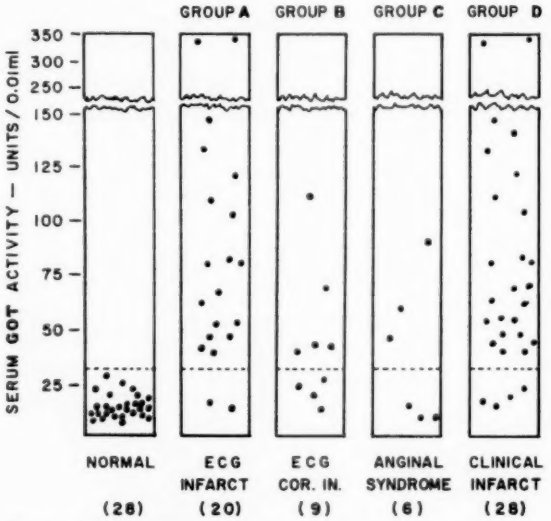

Fig. 2. Serum GOT activities in 40 patients with coronary disease. Each dot represents the highest activity observed in a single patient. Dotted line is the upper limit of normal. Figures in parentheses refer to the total number of patients in a particular category as described in the text.

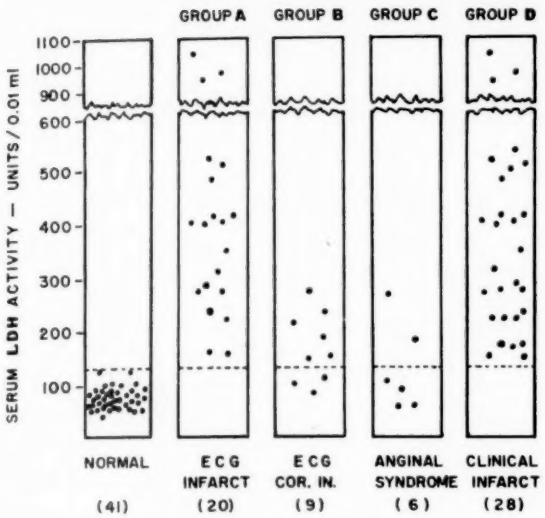

Fig. 3. Serum GPT activities of 37 patients with coronary disease. Each dot represents the highest activity observed in a single patient. Dotted line is the upper limit of normal. Figures in parentheses refer to the total number of patients in a particular category as described in the text.

range (Fig. 3, group C). One case presented a peak elevation of 35 units. Activities were also determined on 26 patients with a clinical diagnosis of myocardial infarction (Fig. 3, group D). Nine of these showed elevated levels with a range from 25 to 75 units.

Discussion

All patients in this study with either electrocardiographic evidence or a valid clinical impression of acute myocardial infarction showed LDH activities that were above the normal range. GOT determinations on these same patients were normal in two of those with electrocardiographic evidence of infarction and four of those with a clinical impression of infarction. These determinations were done several days after the onset of pain when the time-activity curve of GOT might be expected to have declined. Simultaneous GPT determinations on this same group showed more than half to be within normal limits. This would indicate that LDH and GOT activities are much more likely to be elevated during the course of myocardial infarction than is GPT activity.

Nine patients with electrocardiographic evidence of acute coronary insufficiency were studied. The elevated LDH (six patients) and GOT (five patients) activities would suggest that myocardial necrosis occurred in these individuals. A similar conclusion could be drawn in those individuals having an anginal picture associated with elevated transaminase levels.

Summary

Serial determinations of serum LDH, GOT, and GPT were performed on 40 patients with coronary heart disease.

Activity in the serum of LDH and GOT correlated very well with electrocardiographic and clinical evidence of recent myocardial infarction. GPT levels did not correlate with any degree of consistency.

Elevated serum LDH and GOT activities are valuable signs of myocardial necrosis in those patients presenting the clinical and laboratory picture of acute coronary insufficiency or angina pectoris.

It is suggested that elevated serum LDH and GOT levels indicate myocardial necrosis in those patients presenting the clinical and laboratory picture of coronary insufficiency or angina pectoris.

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Role of Emotional Stress Preceding Coronary Occlusion*

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IN THE vast field of coronary disease research, the investigation of precipitating causes of myocardial infarction has drawn comparatively little attention. The question of immediate causation of an attack of coronary occlusion is but rarely posed. At the very best, insight into the circumstances under which coronary occlusion develops and into the mechanisms operative at that time may contribute to its prevention.

It is the purpose of this presentation to review briefly the rather scant literature dealing with the role of emotional factors and life events prior to myocardial infarction, and to report some of our own experiences gathered in the last few years with particular reference to emotional stress and trauma preceding this vascular accident.

HISTORICAL REVIEW

In a study of "coronary occlusion and fatal angina pectoris" Fitzhugh and Hamilton[1] mention preceding emotional strain in 13 out of 100 fatal cases. Boas[2,3] regards emotion as a possible factor and gives two instances in which acute excitement in a 34- and in a 48-year-old man preceded myocardial infarction. He quotes the famous example of John Hunter who felt himself at the mercy "of any rascal who chose to annoy and tease him." Hunter died suddenly at a medical meeting when one of his colleagues flatly contradicted him. Yet Bean[4] in reviewing predisposing and precipitating causes in 300 cases of myocardial infarction makes no mention of emotional factors as a possible cause. Master, Dack, and Jaffe[5] found excitement to precede an attack of infarction in only five instances out of 530! In a later paper[6] excitement has been recognized to have been involved in only 2 out of 100 attacks. They state: "It is now generally accepted that the vast majority of attacks of acute coronary occlusion takes place fortuitously and spontaneously." Blumgart[7] mentions the possibility of reflex factors set into play by emotion and thus acting on the coronary circulation. Paterson[8] admits that emotional stress may be "intimately concerned in the mechanism of coronary artery thrombosis." Kapp[9] takes the view that attention should be given to the amount of physical and emotional stress preceding such attacks. White[10] relates "perhaps acute coronary thrombosis" as a possible result of what may seem to amount to only minor nervous or emotional strain. Applebaum and his coworkers[11] in a recent review of 888 consecutive cases of myocardial infarction refer to emotional excitement as a precipitating factor in 16 cases, stating rather tentatively that "one might accept continuous emotional stress as a contributing factor provoking myocardial infarction."

Most of this information was apparently gathered by reviewing a great deal of case material and possibly only their charts in retrospect rather than by close investigation of individual cases. It appears then that the relationship between emotional strain and coronary occlusion has been realized to a varying degree, but a detached review of the material published gives only little and somewhat controversial (Keys,[12]

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Miller,[13] Arnott[14]) information on the importance of this connection.[15] A definite discrepancy seems to exist between the layman's idea of a "broken heart" and the results of scientific inquiry into the corresponding pathologic condition.

A standard periodical, *Psychosomatic Medicine*, contains only three reports on studies of coronary artery disease within six years, only two thereof referring specifically to coronary occlusion.[16] Arlow,[17] in a much quoted paper on "Identification Mechanisms in Coronary Occlusion," stresses the incomplete, spurious identification of the patients with their fathers, leading to overcompensatory mechanisms of defense, such as compulsive competitiveness, and the traumatic effect of the experience of failure as well as their inability to accept success with due satisfaction for the same reason. "This minor insecurity and sense of weakness which the patient fears to face and which he seeks to deny remain unaffected by realistic achievements." His case histories illustrate such failure resulting in coronary occlusion as one of the few ways out of a situation unbearable to these patients. Our present work had been largely concluded when very recently a more extensive study of the relation of emotional factors to coronary occlusion was published by Weiss and his associates.[18] Our conclusions are quite similar to those of this group; their work will be discussed later.

The study presented here does not attempt to contribute to the relevant psychosomatic question—to be sure, also one of the first order—whether a specific personality pattern, attitudes or a conflict situation is characteristic of people suffering from coronary heart disease. It has been intended here, however, to inquire into the circumstances preceding an episode of coronary occlusion in a group of patients, with particular attention to the role played by emotional stress. These patients do not represent a strictly consecutive series of cases, since some were too ill to be interviewed or died before information could be obtained. In addition to the usual medical history, a life history was taken.

Case Material and Results

Forty-one patients have been studied. In 18, emotional stress could not be considered to have played a role during the months, weeks or days prior to infarction. In seven a strong or unusual physical effort may be considered responsible for the attack. It should be emphasized that in nine patients no precipitating cause could be demonstrated at all.

In 23 patients emotional strain of possible relevance preceded the coronary occlusion. In these patients emotional stress seemed to appear in three different ways: (1) the sudden impact of acute stress likely to disturb the patient's balance (pattern I, 3 cases); (2) a pattern of what could be termed "chronic or subacute" stress followed closely by an experience of acute emotional strain, sometimes of an entirely different origin and nature (pattern II, 11 cases); (3) a mixture of a number of stressful life circumstances with emotional stress as one of its components (pattern III, 9 cases). A few case reports will illustrate these different patterns.

Pattern I. Sudden Emotional Stress as a Precipitating Factor

Case 1. A 47-year-old official had since 1953 been suffering occasionally from pain in his arms after walking about half a kilometer; once when serving as judge in a football game, he had experienced rather severe pain. He had been in the hospital in December, 1954, because of shoulder pain of an unexplained nature. Recently, he had suffered such pains only occasionally. Of late he had difficulties with his landlord, and a Rent Court arranged a settlement between them. The settlement suggested seemed to him quite acceptable and he was ready to pay the agreed sum. When he told his wife about the settlement, she severely criticized him for entering into this agreement. He was upset so badly that he left home hurriedly and in extreme anger, returning late at night. On leaving, he felt severe shoulder pain which increased continuously. Next morning there was slight pain only and he went to work. The day following, while shopping, he experienced severe chest pain and was in a cold sweat. He returned home with great difficulty. The pain subsided but returned with increased violence two hours later. He had developed coronary occlusion.

He emphasized that he was accustomed to suppressing anger and excitement, but these emotions were more violent this time than any he had previously experienced.

Pattern II. Acute Emotional Stress in Addition to Prolonged Emotional Tension

Case 2. A 50-year-old unmarried clerk, whose father had had "angina pectoris" and whose younger

brother also suffered from a heart ailment, had been suffering from an ulcer for many years, particularly the last winter. He had never experienced any chest pain. He had put himself on a rather strict diet and only recently, because he felt much better, had he enlarged his diet including up to 60 g of butter per day.

All his life he had been a rather lonely and peculiar type of person switching from one job to the other, usually looking forward with optimism to the prospects of a new job which, however, never materialized. In the opinion of his elder brother he probably never would make a living. He came from an extremely orthodox Jewish family, a tradition particularly insisted upon by his mother, but had broken away from religious observance completely at the age of 18, and entered the University to study history and philosophy.

Of late, he had been in very precarious circumstances. At a time of great housing shortage and high prices he lived in a small rented room, hard pressed by his landlady to leave. Continuous pressure was exerted upon him, but, as he says, he is a type who is unable to fight back. May 14, 1954, was a day of utmost excitement for him. About a week prior he had met an acquaintance who, aware of his housing difficulties, had raised his hopes by stating that he would be able to help him get a small place of his own, suitable from every point of view. After having been given the promise of quick help, the patient had, after a week of tense anticipation, not heard further from his friend. That afternoon, May 14, he observed a young woman who obviously had moved into the promised apartment, hanging out the washing. Bitterly disappointed, a few hours later he was struck by severe chest pain, cold sweat, and the typical symptoms and signs of coronary occlusion.

Further interviews brought out an ambivalent attitude toward his extremely religious mother, whose physical beauty he repeatedly emphasized and whom he had visited, walking across town twice daily for many years, until her death at the age of 80 in 1947. He considered his father a very gifted individual, who was broken by some misfortune in his youth, lacking proper education in order to make a career, "a most charming sort of individual." The impression was gained that he identified himself closely with his father.

Immediately following the first interview, a few weeks after the patient's myocardial infarction, he felt chest pain and started to cough. Cyanosis and stasis of both lung bases appeared; he broke out in cold sweat, and only by administration of Pantopon could development of frank pulmonary edema be prevented.

Case 3. This was a 46-year-old owner of a small factory. His eldest brother died at the age of 60 from a heart attack, and a 48-year-old brother had had an attack of myocardial infarction a year previous. Their father had suffered from asthma. The following history was obtained from the wife of the patient.

They had been married for 15 years. There are no children. Nine months previously, the patient developed sudden signs and symptoms of diabetes and his blood sugar at that time was 295 mg %. His physical condition deteriorated considerably, although his diabetes was controlled by diet and insulin. We were informed later that diabetes had developed when his wife, at that time on vacation abroad, had written to him that she had decided not to return and would obtain a divorce. On his insistence and emphasis of his acute disease, she had finally returned. He was in the habit of drinking much coffee and smoking about 40 cigarettes a day.

Financial difficulties developed when he had invested a great deal of money in his business and an important client, usually a large buyer, did not keep his promise to buy and pay at once. At about the same time friction and disputes occurred with his workers. At least one of them started to use, without the patient's knowledge, a truck for haulage at night on the patient's account. The patient was thereby forced to bear expenses for repairs until, properly warned, he trapped the worker at night on the highway. The situation led to a violent discussion with the driver and five others threatening him physically.

During these same weeks the patient had great difficulty in coming to terms with the income tax authorities; he believed that his workers had betrayed him. A month previously an attempt had been made to attach some belongings of his, which caused him great tension. Since then just the ring of the doorbell caused the patient to become excited. One day, the treasury agents, as the family supposed, through the treachery of his workers, came to search his house. At the same time, 10 guests from out of town were assembled in another room of his apartment. The patient tried to cover up the situation, which was a shocking experience to him. He went on to play cards with his guests until two o'clock in the morning, and astonishingly enough, felt rather well during the next day. At 8 o'clock the following morning he was attacked by severe chest pain, palpitation and sweating; a typical coronary attack had ensued.

During his stay in the ward we were impressed by his emotional lability, although he described himself as a "cold-blooded individual"; he cried easily, and according to the description of others, must have been a rather tense, emotional, occasionally daring type of individual all his life.

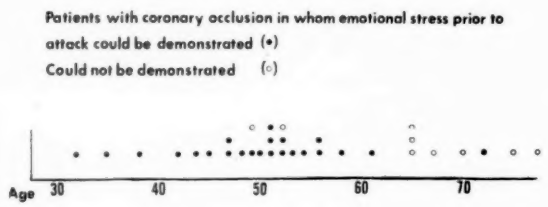
PATTERN III. EMOTIONAL STRESS CONTRIBUTING TO MULTIPLE STRESS PATTERN

Case 4. A 56-year-old professional man, a tourist in Israel, whose mother suffered from diabetes, had never had any anginal pain. In recent months there had been considerable tension: a larger home was purchased at his wife's initiative and against his will, a "living up to the Joneses" affair; another family topic had caused friction and disagreement between the two, and finally after considerable argument he reluctantly undertook a trip to Europe and Israel. They had traveled rather fast, quickly visiting many places and

had arrived in mid-summer. The morning following their arrival they made a round trip through Jerusalem, closing with a visit to Mount Zion, a strenuous undertaking for the particularly hot day it happened to be. He was then and there attacked by violent chest pain and a typical attack of coronary occlusion ensued.

Discussion

The first group of patients, those who experienced a coronary occlusion closely following an emotional trauma, comes closest to common understanding and accepted ideas. It seems, however, that the second group is the one of greater significance, statistically as well as psychophysiologically: here, after a build-up of tension and a period of emotional strain, usually of high degree, the individual, in an already weakened condition, is subjected to the sudden and severe impact of a new emotional injury. This pattern is known to physiologists, psychologists, and psychiatrists as particularly injurious, as Arlow states, quoting Freud in this context. It deserves particular emphasis that this latter pattern of subacute and acute superimposed injury seemed to occur much more frequently among the younger people than in the older age group, in which frequently no precipitating factor could be discovered at all. The graph below illustrates this particular age distribution.


Patients with coronary occlusion in whom emotional stress prior to attack could be demonstrated (•)
Could not be demonstrated (○)
Age 30 40 50 60 70

Weiss and his associates[18] in their recent publication have made strikingly similar observations and obtained figures very like ours. Physical stress could be shown to precede six attacks of coronary occlusion; "gradually mounting tension" was discovered in 21 of their 43 patients and interestingly enough, they were also impressed by the fact that in people below 60 years of age emotional factors could be demonstrated to a much larger extent than in those above 60. The "anniversary reaction" observed by them in four, possibly in another five instances, was seen in our subjects clearly only twice. One of them, J. E., a 51-year-old man, long separated from his only brother, the only member left of a large family, was reunited with him. Together they attended synagogue for memorial services for the war dead and the victims of persecution. The patient became ill on his way to the services.

In the course of the investigation of our patients and a number of others who are not included here, two additional observations were made which, if borne out by further study, may have a certain relevance for the understanding of the onset of coronary occlusion. There frequently seemed to be a lag in time of anywhere from a few up to about 36 hours between the precipitating event, whatever its nature, and the onset of the full-blown clinical picture of infarction. This phenomenon may have its explanation in certain pathologic processes as hemorrhage or incipient thrombosis, which after being initiated will take a certain time to lead to complete occlusion of a coronary vessel.

Patients have been seen in whom a depressive mood preceded recognizable symptoms and signs of coronary occlusion; a physician-patient of ours correctly predicted his third coronary attack, having perceived, for the third time, a let-down feeling and depression so familiar to him from the two previous occasions.

Importance of other stress factors

The fact that in a considerable number of instances emotional stress seems to play no role or at least cannot be demonstrated to do so, does not, of course, yet lump all these cases into one or for that matter a homogeneous group. On the contrary, here, in our material as well as in that of others, we meet a variety of circumstances commonly quoted as preceding if not provoking myocardial infarction, i.e., overexercise, undue fatigue, sexual overactivity, exaggerated smoking, and other factors. We have been particularly impressed by the fact that in 8 of our 41 patients travel from the sea coast to Jerusalem, 800 meters above sea-level, or in the reverse direction, preceded the attack of coronary occlusion by only a number of hours. To what extent rapid adjustment may provoke coronary thrombosis in susceptible

individuals or represent at least the famous last straw on the camel's back, is by no means clear. The influence of sudden weather changes seems also to play a role at least according to observations in our city, where over the years, peaks of incidence of coronary occlusion can be demonstrated during the hottest, the coldest, and the climatically most unstable season.

Each factor presumably involved in the etiology of coronary thrombosis should be studied by itself; it is equally obvious that it cannot always be quantitatively evaluated. In the case of J. G., for instance, a 54-year-old man, recently recovered from depression, which should be considered the main factor precipitating coronary occlusion—30 cigarettes consumed in one evening during a game of cards, a trip from the sea coast to Jerusalem on the following morning, or finally, the attempt to participate in the memorial meeting for his son who had been killed in the recent war? This case obviously belongs in pattern III as described above. Considering psychologic etiology ought not to be regarded as excluding other factors on an "either-or" basis, but rather as a way of enlarging our scope and understanding, sometimes thus focusing on the main factor.

The impact of events on man and their possible stress-producing action can be measured and interpreted only in terms of this man's personality and previous experience; whether the blow hurts does not depend only on its vigor. We have tried to interpret our material guided by this idea. That an experience as common and customary as medical rounds in a hospital ward may represent an emotionally heavily loaded situation is proved by Jarvinen's[19] interesting observations on not less than six patients with coronary heart disease who died during rounds in his ward, within a few years. We have unfortunately also lost two patients suffering from this disease during medical rounds.

It appears then that under certain conditions, among which genetic predisposition plays a preeminent part and certain types of nutrition play a probable major contributory role together with other factors, acute, and even more so prolonged, emotional stress followed by an acute emotional impact or such stress combined with other factors is able to produce coronary occlusion, usually of a thrombotic nature.

EMOTIONAL STRESS AND THROMBOGENESIS

Cannon[20] has shown that irritation and excitement make cats' blood clot quicker, and Schneider,[21] Macht[22], and ourselves[23] have made analogous observations in man. We have of late observed a number of individuals who could be considered to be under chronic stress and who then showed short coagulation times in siliconized tubes usually together with eosinopenia. We have observed the stress response of eosinopenia[24] and decrease of the coagulation time using this technique in students during their examinations,[23] after stress producing interviews, after administration of corticotropin and cortisone,[25] as well as at the very beginning of a thrombotic process. Emotional stress in addition, especially anxiety, is known to increase cardiac output and to be able to increase peripheral resistance, thus putting an additional burden on an already diseased heart.[26,27]

At least one pathologist of rank, Duguid,[28] stresses that in patients who die at an early age from coronary thrombosis the vascular changes are small. He suggests that they are produced by thromboses, rather than the thrombosis being due to the vascular changes, an opinion held by Rokitansky many years ago, and today shared by others. Morris[29] has explained, on the basis of statistical and pathologic evidence, that coronary thrombosis has been on the increase in England and Wales, whereas atheroma has not, and even may have become rarer in recent years. The experiences presented here, limited as they are in number, allow us to establish a working hypothesis. In elderly people coronary occlusion may be the consequence, sometimes scarcely avoidable, of severe atheromatosis of the coronary arteries and minor influences may provoke their occlusion in addition to the conspicuous pre-existing lesions. In younger people, on the other hand, many of the coronary occlusions may represent primarily a disturbance in blood coagulation or in the wider sense a thrombotic disorder. This condition may frequently be provoked by a state of emotional stress and strain as de-

scribed above. "Thrombogenesis" seems to prevail in its relative importance in the younger age groups over "atherogenesis" and matters may be reversed in the older age groups. The two mechanisms may be jointly responsible in many cases.

Such evaluation of possible factors is a necessary prerequisite for a preventive approach to coronary artery disease, since the means to forestall thrombosis in a given individual are obviously different from the ones by which ultimately severe atheromatosis might be prevented.

Summary

In an attempt to determine the role of emotional factors as precipitating causes of coronary occlusion, 41 patients, recent victims of the disease, were studied.

In 23 patients a well-substantiated history of emotional stress prior to infarction was elicited. Three patterns of such stress could be demonstrated: (1) acute short-term stress (3 cases); (2) chronic or subacute stress, frequently complicated by acute stress immediately prior to coronary occlusion (11 cases); and (3) emotional stress as a contributory factor to other stress mechanisms (9 cases).

Emotional stress could be more frequently shown to precede coronary occlusion in younger than in older people.

It is suggested that thrombogenesis be distinguished from atherogenesis in order to further better understanding of coronary artery disease and coronary thrombosis; thrombotic tendency may be of decisive influence in coronary occlusion in the younger age group as potentially precipitated by stress mechanisms operating on blood clotting; atherogenesis, on the other hand, represents the aspect of a usually slow vascular degenerative disorder which has to be attacked mainly on a long-term basis.

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Cardiovascular Disease in Psychotics

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THERE has been a trend in the last 15 years to view a patient as a whole organism rather than as a group of related organ systems. This is evident in scientific and lay publications, but the trend is not very extensive and is in many instances superficial, even though "psychosomatic" has now entered the vocabulary of the layman as well as of professionals. For 20 years this writer has been interested in the interrelation between psyche and soma and would see nothing incongruous were the work of Sigmund Freud[1] and Walter B. Cannon[2] to be amalgamated; amalgamated, that is, so that the mixture would preclude separation of the components.

The biologic psychology of Adolph Meyer is a long way from the taxonomic work of Kraepelin; and the physiology of the kidney as described by Homer Smith is again a long way from the static anatomy of the middle ages. But are not all these workers studying different aspects of the same organism, the patient? How does a cat, standing on a fence and snarling at a dog below, differ from a cat in Cannon's laboratory; or differ from the patient on Freud's couch; or differ from the patients on whom Grinker and Spiegel used narcosynthesis? The answer of course is that the difference lies only in the degree of reaction permitted by the biologic complexity of the animal in question, as modified by the specific environment.

There is no room for speculation on the old "nature versus nurture" level. It becomes necessary to accept the individual as he is and in his particular surroundings in order to study him objectively.

A whole host of biologic situations have been described by Dashiel[3] in his *Fundamentals of Objective Psychology* and these situations lend color and credence to the theorem that the organism must be studied as a biologic unit in its particular environment. This goes for the human animal particularly. Homo sapiens with his complicated nervous system and complex endocrine system living in today's culture is no longer a simple "receptor-connector-effector" unit.

The differences between Cannon's cats, Freud's neurotics, and the combat casualties of Grinker and Spiegel are obviously small when one considers the development and complexity of the animal unit involved. The man with tachycardia every time his boss approaches, and the woman with backache nothing seems to relieve "Except a good hug from my husband," cannot be divided among physicians interested in various organ systems.

Serving as cardiologist to a psychiatric hospital, the author observed an incidence of cardiovascular disease among the hospitalized patients which appeared significantly above the expected incidence. A diligent search of the literature of psychiatry and pathology revealed no writings on this topic. An exhaustive study of the *Index Medicus* through the years 1940 to 1952 did not reveal a single article written on just this topic. With all the study and writing on heart disease no one had thought to study the mutual operational aspects of these two important derangements of bodily function.

Therefore, this observation of an apparently high incidence of heart disease in psychotic individuals with an opportunity to examine many hundreds of patients, prompted studies to determine the actual incidence of cardiovascular disease in psychotic individuals. That certain information might also be derived concerning an etiologic relationship between cardiovascular disease and mental disease was a secondary consideration. It would have been premature, at this stage, to indicate a causal relationship. However, evidence relating to the pathogenesis of cardiovascular or mental disease

may develop from studies such as this. Breutsch,[4] indeed, has already cited an example of this type of investigation.

Population Studied

The writer served as cardiologist to the Veterans Administration Hospital at Lyons, New Jersey, for seven years starting November 1, 1946. This hospital is primarily a psychiatric hospital serving New Jersey and parts of New York and Pennsylvania. As usual, a large number of patients had been hospitalized for many years. Since the population was stable, this group of patients furnished an unusual opportunity to study the relative incidence of cardiovascular diseases in psychotic individuals. This was a selected group of men because some screening had been done prior to their service with the armed forces. In this way, a number of men with rheumatic heart disease might have been eliminated prior to entry into military service.

As in most psychiatric hospitals, there was a higher incidence of central nervous system syphilis than is found in the population outside such institutions and similarly cardiovascular syphilis was more frequent. Also, in such a psychiatric hospital there is an unavoidable tendency to accumulate patients with psychoses due to arteriosclerotic and hypertensive cerebrovascular disease.

A special opportunity for study presented itself during the winter 1947–48. At this time, a team of physicians performed annual physical examinations. That is, all patients hospitalized more than one year were examined. The author personally examined the cardiovascular system of each patient. The data were transferred to punch cards and subsequently correlated and tabulated. No women were included in the group studied since the hospital did not ordinarily accept female psychotics.

From the cardiovascular point of view, this group of veterans resembled closely the population in any other large public mental hospital except that the group was limited to males and that there had been some previous screening for rheumatic heart disease in the preinduction physical examinations. No attempt was made to separate arteriosclerotic heart disease from hypertensive cardiovascular disease where both were present. If a patient had evidence of both he was indexed only once. This same rule also applied to other combinations of cardiovascular diseases listed below; they were not doubly listed.

TABLE I

Psychiatric Causes of Admission*

Psychiatric diagnosis	%
Schizophrenia	32.0
Psychosis with central nervous system syphilis	0.8
Psychosis with arteriosclerosis or hypertension	1.8
Psychosis with alcoholism	3.7
Paranoia	0.30
Involutional melancholia	0.40
Psychoneurosis	22.0
Non-neuropsychiatric	15.0
All others	23.0

* Personal communication, Dr. Nathan Kline.

Criteria of Cardiovascular Disease: In many instances the history was incomplete because the patient's psychosis prevented his relating details. The usual physical standards served as criteria. Hypertension was recorded if the systolic pressure was above 150 and the diastolic above 90. Each patient had a radiographic examination of the chest, and many patients had a fluoroscopic examination. Every patient had a urinalysis. All patients over 40 years of age had electrocardiograms and many of those under 40 had had routine electrocardiograms prior to electroshock therapy. All who had a history or physical findings suggestive of cardiovascular disease at the time of the annual physical examination had electrocardiograms. However, the diagnosis of cardiovascular disease was not based on the electrocardiogram alone except for the rare instances of typical classical myocardial infarction.

Patient Material: As a result of the annual physical examination, a group of 1,558 patients were studied. This included 1,486 white males and 72 Negro males. The latter are not included in the following discussion because of the disproportionately small number. It is well known that there are differences in incidence of heart disease in the white and Negro

races, e.g., syphilis. When the clinical psychiatric diagnosis was psychosis due to cerebrovascular disease, it was noted as such, but when the diagnosis was senility, the patient was not included in the study. It is customary for some senile patients to be hospitalized in institutions such as this. Sufficient information was available for study of 1,230 white patients; their current diagnosis included, for each, a specific psychosis that required continued hospitalization.

Table I indicates the causes for admission to this hospital during a typical 12-month period in 1948–49. Schizophrenia was the most frequent cause of admission. Table II indicates the causes for continued hospitalization (psychiatric diagnosis) of the patients examined and later studied for incidence of cardiovascular disease. That is, Table II lists the current psychiatric diagnosis of the 1,230 white patients studied.

After comparing the causes of admission (Table I) with the causes for remaining in the hospital (Table II), it is evident that patients with schizophrenia tend to remain in the hospital. That is why schizophrenics compose the largest group in this study. The second largest group is that of psychotics with central nervous system syphilis and the third largest is that with arteriosclerotic or hypertensive disease producing psychosis. The data reported above are in accord with those published by Frankel.[5] He, too, found schizophrenia the most common cause for continuous hospitalization of mental patients, although he found psychosis with cerebral arteriosclerotic and senile brain disease the most common cause for first admission to state mental hospitals in New Jersey; while Kline found schizophrenia the most common cause for admission in the patients at this particular veterans hospital.

TABLE II

Psychiatric Causes for Continued Hospitalization
1,230 white patients

Psychiatric diagnosis	Number	%
Schizophrenia	947	76.0
Psychosis with central nervous system syphilis	159	13.0
Psychosis with arteriosclerosis or hypertension	66	5.3
All others	58	5.7
TOTAL	1230	

TABLE III

Deaths from Cardiovascular Disease
133 white male psychotic veterans

Antemortem psychiatric diagnosis	Total number of patients	Cardiovascular deaths
Schizophrenia	48	19
C.N.S. syphilis	24	11
Psychosis with cerebrovascular disease	35	18
All others	26	7
TOTAL	133	55

It should be remembered, however, that Frankel reported data from state psychiatric hospitals. In New Jersey, as elsewhere, these state institutions are often the recipients of patients who are social rather than medical problems—in short, patients thrust on the state institutions because of rejecting family attitudes—and for this reason the statistical data may be varying.

Autopsy Material: In another approach to this same problem of cardiovascular disease in psychotics, material was obtained from reports of postmortem examinations on patients hospitalized at this same institution. All autopsy protocols from January 1, 1947, to December 31, 1951, were reviewed. Some patients therefore were included in both the live study and the review of deaths. There were 391 deaths in this five-year period and postmortem examination was performed in 255 instances. Twenty-three Negro patients were autopsied, as were also some employees and nonpsychotic patients. There were 133 postmortem examinations on white male veterans for whom antemortem diagnosis of chronic psychosis had been recorded.

The antemortem diagnosis of psychosis with central nervous system syphilis, paranoia, manic depressive psychosis, schizophrenia, etc., was accepted only if the diagnosis was unequivocal. Therefore, each of this group of 133 veterans

was considered to be frankly psychotic (chronic psychosis) by the psychiatric staff of the hospital.

The usual anatomic criteria were employed; gross pathologic evidence of disease was required for inclusion of a patient in the group with cardiovascular disease. The pathologist doing the autopsies had no idea that, at a later date, the information obtained would be included in such a study as this.

Table III reveals the number of deaths from cardiovascular disease as decided by the pathologist at the autopsy table. In addition to cardiovascular disease, tuberculosis, other infections, and neoplasms were prominent as causes of death. This is in accord with previous experience in psychiatric institutions.

This study, however, was designed to determine the incidence of cardiovascular disease in members of the group studied, rather than the frequency of cardiovascular disease as the primary cause of death. Therefore, the data from 133 autopsies were studied to determine the total incidence of cardiovascular disease. The findings will be detailed below.

Cardiovascular Disease and Schizophrenia

There were 947 live white male schizophrenics, chronically hospitalized, who were examined for incidence of cardiovascular disease. Table IV indicates the incidence of clinical cardiovascular disease in this group. Both known and newly discovered cases are included.

In the schizophrenic group less than 41 years old (210 patients) there were 3.3 per cent with rheumatic heart disease and 2.3 per cent with arteriosclerotic or hypertensive cardiovascular disease. None of the schizophrenics under 41 years of age exhibited clinical evidence of syphilitic cardiovascular disease. After grouping the schizophrenic population above 41 years of age, it became evident that 24 per cent (142 out of 589) had arteriosclerotic or hypertensive cardiovascular disease.

The graph in Figure 1 depicts rather dramatically the incidence of arteriosclerotic and hypertensive cardiovascular disease in white male schizophrenics. It allows a comparison with the general population of the United States. The figures used for a basis of comparison were taken from the U.S.P.H.S. *Public Health Reports.*[6] These figures derived from the National Health Survey 1935–36 are not race specific. Correspondence with the U.S.P.H.S. indicates that the general population figures would be lower should whites only be included. They would be further lowered if arteriosclerosis and hypertension alone had been listed.

A statistical comparison of the incidence rates is corroborative. The computations are listed in Table V. The probability that random samples of the U.S.P.H.S. population survey used (equivalent in numbers to the Lyons samples), would yield incidence rates as different as the Lyons samples is, for each age range, less than one in a thousand. That is to say the

TABLE IV

Clinical Cardiovascular Disease in 947 Live Schizophrenic Patients

Age	Cardiovascular disease			No disease	Total patients
	Rheumatic	Syphilitic	Arteriosclerotic and hypertensive		
Less than 31	3	–	3	105	111
31–40	4	–	2	93	99
41–50	2	2	21	149	174
51–60	–	1	102	408*	511
61–70	–	1	16	30	47
71–80	–	–	3	2	5
Total patients	9	4	147	787	947

* One patient with congenital heart disease attached to this group.

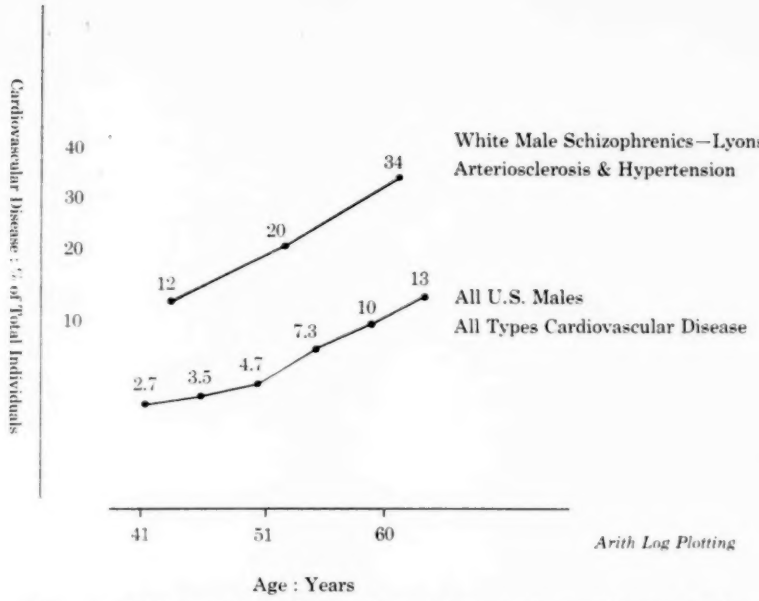

Fig. 1. Incidence of arteriosclerotic and hypertensive cardiovascular diseases in white male schizophrenics compared with the general population.

chance of errors due to sampling is less than one in a thousand (computed by Louis Delman, PH.D., V. A. Hospital, Lyons, New Jersey).

It is readily seen that the incidence of arteriosclerotic and hypertensive cardiovascular diseases tends to increase with age in both the schizophrenic group and in the general population. The incidence of arteriosclerotic and hypertensive cardiovascular disease was significantly greater in this group of schizophrenics than in the general male population of the United States.

There were 48 autopsy examinations on white male schizophrenics. On postmortem study, cardiovascular disease was found in two-thirds of these. Twenty-six had arteriosclerotic, rheumatic and hypertensive cardiovascula-disease, and one had endocarditis. Reference to Table VI will reveal that the over-all inr cidence is great. Further, the age-specific rate in the bracket 51 to 60 years of age at the time of death is high. That is, 18 out of 28 white male schizophrenic veterans in this age group had gross pathologic evidence of arteriosclerotic or hypertensive cardiovascular disease or both on autopsy examination.

Cardiovascular Disease and C.N.S. Syphilis

There were 159 white males with a psychiatric diagnosis of C.N.S. syphilis. Only 6 per cent

TABLE V

Comparison of Incidence of Cardiovascular Disease in Lyons and U. S. A.

Age	Number of Lyons patients	Lyons rate (%)	Observed frequency	Population rate (%)*	Expected frequency	Chi square
41–50	174	12	21	3.5	6.09	38.8
51–60	511	20	102	7.3	37.3	123.0
61–70	47	34	16	13.0	6.11	19.1

Chi square value for 1 d.f. at 0.01 level—6,635.
Chi square value for 1 d.f. at 0.001 level—10,827.
* Highest reported rate within given age range (Fig. 1).

TABLE VI

48 White Male Schizophrenics Autopsied
Incidence of Cardiovascular Disease

Age	Cardiovascular disease					Total patients
	Arteriosclerotic and hypertensive	Acute endocarditis	Rheumatic, arteriosclerotic, hypertensive	Total	None	
21–30	1	—	—	1	2	3
31–40	—	—	—	—	2	2
41–50	3	1	1	5	4	9
51–60	17	—	1	18	10	28
61–70	3	—	—	3	1	4
71–80	2	—	—	2	—	2
Total	26	1	2	29	19	48

(10 out of 159 patients) were found to have syphilitic heart disease. It should be remembered that in syphilis there is a rapid, early, and wide dissemination of treponema throughout the body. The heart is included. There is a long latent period during which syphilis of the central nervous system and of the heart may not be suspected. Another factor to be considered is the frequency of symptomless infection. An incidence of 6 per cent syphilitic heart disease in a group of 159 patients with central nervous system syphilis should be considered rather low. If this incidence is lower than expected it should be remembered that these patients were all veterans and had all been treated for syphilis, although some were treated late rather than early. It should also be remembered that most of them were World War I veterans and treated in the days when antisyphilitic therapy was less satisfactory than it is today. Nevertheless, the figures were surprisingly low. Fourteen per cent (22 out of 159 patients) had arteriosclerotic or hypertensive cardiovascular disease or both, without clinical evidence of syphilitic cardiovascular disease. None had rheumatic heart disease. New and old cases are included.

There were 24 postmortem studies done on the patients with antemortem psychiatric diagnosis of C.N.S. syphilis. Nine patients were found to have arteriosclerotic or hypertensive cardiovascular disease or both. Four patients had gross pathologic stigmata of syphilitic heart disease; three had stigmata of syphilis plus arteriosclerosis or hypertension; one had stigmata of syphilis and rheumatic heart disease; one patient had bacterial endocarditis and the remaining six were normal.

Cardiovascular Disease and Arteriosclerotic Psychoses

There were 66 white males continuously hospitalized for arteriosclerotic psychoses who were studied for incidence of cardiovascular disease. Both known and newly discovered cases were included. Of course the factor of aging must be taken into consideration. Certainly atherosclerosis increases with age. But, it is well known that the atherosclerosis of age varies tremendously from one individual to another; and further, the degree of atherosclerosis varies from one organ or part of an organ to other organs or parts. Forty-two per cent (28 out of 66 cases) had arteriosclerotic or hypertensive cardiovascular disease, or both. Two patients had stigmata of syphilitic heart disease.

There were 35 postmortem studies done on patients with antemortem diagnosis of psychosis with arteriosclerosis or hypertension. Autopsy examination revealed a high incidence of cardiovascular disease (86 per cent) in the group labeled "Psychosis with Arteriosclerotic and Hypertensive Cardiovascular Disease." There were in fact 23 patients with arteriosclerotic and hypertensive cardiovascular disease and 6 patients with that plus syphilitic cardiovascular disease;

one patient had syphilitic cardiovascular disease alone. The remaining five had no evidence of cardiovascular disease. No doubt some of the patients suffered primarily from cardiovascular disease, with a secondary psychosis accounting for the continued hospitalization. Certainly, the aging of these patients must have been a contributory factor to the cardiovascular disease and therefore indirectly to the psychosis.

It is no surprise to find that when arteriosclerosis and hypertension are associated with severe psychosis, equivalent to severe brain disease, extensive heart disease of similar type is also present.

Discussion

After considering the data presented above, it becomes evident that additional study of the interrelationship of mental disease and heart disease is necessary. Direct evidence is very scarce; little has been done in research on this problem and even less written. Not all that has been written can be accepted literally. Current textbooks[7] subscribe to popular views: "Schizophrenia is, however, infrequently associated with heart disease and the protected life of its victims seems to guard them from early onset of so-called degenerative type of heart disease."

The plain fact of the matter is that cardiologists have not studied psychotic patients and psychiatrists have not been interested in the structural diseases to which their patients have been subject. Let us discuss the comment on the protected life of the schizophrenics. There is a tendency to confuse appearance with fact. For the purpose of clarity, let us limit the discussion briefly to a category of schizophrenics known as catatonics. These represent a distinct clinical syndrome, psychiatrically, and are celebrated for their waxy flexibility and calm appearance. Inactive, these people are apt to remain motionless for hours at end, while oblivious to the world around them. But, how many psychiatrists or internists have troubled themselves to determine the pulse of these people. It has been my experience that they normally have a tachycardia which belies their outward appearance. They are in fact very disturbed, very busy people; very active in their internal milieu as evidenced by the pulse rate. There is no reason why catatonia should be considered different from any other response to a stress situation.

If a cold pressor test can produce a tachycardia, why should one be surprised that an emotional situation could produce a tachycardia or hypertension? Armstrong,[8] in studying Air Force applicants, found a high correlation between hypertension and emotional instability (psychometric evaluation) in healthy young men. Best and Taylor[9] citing from MacWilliam (source not given) report that a quiet restful sleep produces a drop in blood pressure but that if the sleep is disturbed, the blood pressure rises.

It would be considerably more correct to say that people with psychosis resulting from central nervous system syphilis are less apt to develop degenerative types of heart disease. In paresis and tabes, as well as in meningovascular syphilis, there is classical destruction of nervous tissue; one finds euphoria, and these patients may be said to be sheltered from life after their disease had produced its destruction. The findings reported above are in accord with such a theory, were it to be propounded.

It has been shown by Ranson and Billingsley[10] that electrostimulation of certain points in the floor of the fourth ventricle with needle electrodes caused predictable rise or fall in blood pressure. Centers for control of blood pressure have been postulated in the hypothalamus and cortex. According to Best and Taylor,[9] the following effects may be noted upon the administration of epinephrine to humans: dilatation of the pupils, protrusion of the eyeballs, gooseflesh reaction, tremor, and sweating. No one could deny that these are findings typically considered indicative of emotional disturbance. They also report that epinephrine has been found experimentally capable of eliciting the following body changes: increase in heart rate and blood pressure; increase in blood volume and red blood cell count; increase in coagulability of blood. Certainly, the changes in blood count, blood volume, and coagulability might predispose to increased vascular thromboses. The increase in heart rate and blood pressure might also, persisting over a long period of time (albeit intermittently), predispose to vascular damage.

Some additional evidence in humans may be reviewed profitably at this point. In a study of transient hypertension, conducted by reviewing reports of annual physical examinations of United States Army officers (performed between 1924 and 1941) Levy *et al.*[11] found "at all ages, sustained hypertension developed more frequently in those with previous transient hypertension than in those who never showed an elevation of blood pressure. In both groups, the rate increased with advancing years." And again, "The death rate with cardiovascular-renal disease was also higher in those with transient hypertension; the figures rose in the older age groups." In a similar study of transient tachycardia, involving the same group of subjects, these same authors found that people with transient tachycardia showed higher rates for later sustained hypertension than did the control group. When both transient tachycardia and transient hypertension were present, the incidence of later sustained hypertension was even greater than when one of the transient conditions was noted. In a group with sustained tachycardia, the death rate with cardiovascular renal disease was considered excessive. They concluded: "Transient tachycardia due to emotional disturbance or some other cause not discernible, like transient hypertension of similar origin, is often a precursor of hypertensive cardiovascular disease."

Summary

(1) Schizophrenia is the most common cause for continued hospitalization in psychiatric hospitals.

(2) Clinically, arteriosclerotic and hypertensive cardiovascular diseases are more prevalent in hospitalized schizophrenics than in the general population outside such institutions.

(3) A high incidence of arteriosclerotic and hypertensive cardiovascular disease was found in the schizophrenics examined postmortem.

(4) Clinically, a low incidence of arteriosclerotic and hypertensive cardiovascular disease was found in a group of psychotics with C.N.S. syphilis.

(5) Clinically, a high incidence of arteriosclerotic and hypertensive cardiovascular disease was found in psychoses associated with arteriosclerosis and hypertension.

(6) A high incidence of arteriosclerotic and hypertensive cardiovascular disease postmortem was found in patients with psychoses associated with arteriosclerosis and hypertension.

(7) On the basis of the evidence presented above and drawn from such varied sources as (a) studies of live psychiatric patients and (b) autopsies on psychiatric patients, one can only come to this conclusion: The psychiatric disorders producing implicit and then later overt physiologic changes may eventually lead to structural changes, to the extent that psychiatric disorders may be partially responsible for cardiovascular diseases.

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The Mortality from Arteriosclerotic and Hypertensive Heart Diseases in the United States

II. Possible Relation to Industry

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IN a previous communication[1] I showed that the mortality rates from arteriosclerotic and hypertensive heart diseases vary markedly in different parts of the United States. With some exceptions, there appears to be a relation between the concentration of population per square mile, the percentage of people living in urban regions and the mortality rates from arteriosclerotic heart disease: The higher the concentration of people per square mile and the greater the urban population in a given state the greater is the mortality rate in that state. There also appears to be some relation between the average per capita income in a given state and the mortality rate from this disease: The higher the income the greater the mortality rate. No definite relationship appears to exist between the death rates from hypertensive heart disease and the concentration of population or the income per capita.

One of the possible causes suggested for the variations in the mortality rates was a difference in the extent of the concentration of industry in the various states. It was felt that inasmuch as most of the industrial establishments are concentrated in urban and suburban areas this factor would at least partly explain the relationship. To substantiate this assumption a statistical study was made of the concentration of the major manufacturing establishments in this country in relation to the mortality rates from these diseases. This paper covers such study.

METHODS OF STUDY

The study is based on an analysis of the major manufacturing establishments in the United States.[2] The products they produce embrace practically all essentials in modern life. They consist of foods and kindred products, tobacco, textile and mill products, general apparel, lumber and wood products, furniture and fixtures, paper and pulp products, printing and publishing, all chemical products, petroleum and coal products, leather products, stone, clay and glass products, rubber products, metal industries and fabricated metal products, electrical and other machinery, transportation equipment, various instruments, other miscellaneous manufacture, administration and auxiliary establishments. The majority of these manufactures are necessarily confined to indoor plants. Those occupational pursuits where activities are carried on mainly in open spaces, as agriculture, fishing, farming, livestock raising, and others, are omitted from our study.

The manufacturing establishments used in our study were found to vary greatly in different states. Inasmuch as the area of each state likewise varies markedly,[3] the number of square miles of each state was divided by the number of factories in that state. This gives us on the average the number of square miles per factory establishment. A classification was then made of the different states according to the following groupings: Group I, those states with one factory in less than 5 square miles; group II, states with one factory per 5 to 10 square miles; group III, those with one factory per 10 to 20 square miles; group IV, those with one factory per 20 to 100 square miles; and group V, those with one factory in over 100 square miles.

The mortality rates from arteriosclerotic and hypertensive heart diseases received similar classifications per state and per group. The average number of miles per factory as well as the average mortality rates from the two forms of heart diseases in each of the above groups

of states were then computed for comparison. The results are shown in Table I.

Observations

It will be observed from the figures in Table I that, with some exceptions, there is a definite arithmetic relation between the concentration of manufacturing establishments and the mortality rates from arteriosclerotic and hypertensive heart diseases, particularly the former. This is shown especially when we compare the high concentration of manufacturing establishments in group I with the very low concentration of such establishments in group V. Thus, with an average concentration of manufacturing establishments of one per 2.2 square miles in group I, the average mortality rate for arteriosclerotic heart disease is as high as 257.7 per 100,000 population and for hypertensive heart disease 68.9 per 100,000 population. On the other hand, in group V, where the average concentration of manufacturing establishment is only one per 284.4 square miles, the mortality rate from arteriosclerotic heart disease is only 156.1 per 100,000 population and from hypertensive heart disease 31.0 per 100,000. It will be observed also that these relationships are true for each group of states. The smaller the average concentration of manufacturing establishments in a given group the lower the average mortality from these diseases in that group. There is an exception in the mortality rate from hypertensive heart disease in group II where the average rate is 54.0 per 100,000 population, which is lower than in groups III and IV. However, for arteriosclerotic heart disease the diminution in each group is progressive and corresponds exactly to the progressive diminution in the number of manufacturing establishments in the given areas.

It will also be observed that in group I, with the highest concentration of manufacturing establishments, the mortality rate from arteriosclerotic heart disease in each state is related fairly closely to the concentration of manufacturing establishments in the given state. Thus, Massachusetts, Rhode Island, New York and New Jersey, with one manufacturing establishment for less than one square mile and Connecticut for slightly more than one square mile, have higher mortality rates from arteriosclerotic heart disease than all the rest of the states in that group. The rest of the groups of states do not show such persistent parallelism between the concentration of industry and mortality rate in each individual state, although the average for all states in the given group shows

TABLE I

Manufacturing Establishments and Mortality From Arteriosclerotic and Hypertensive Heart Disease in the United States

States	Manufacturing establishments (1947)		Cardiac death rate per 100,000 population (1950)	
	Number	Sq. mi. land area per mfg. estab.	Arterio-sclerotic	Hyper-tensive
Group I				
Maryland	2,824	3.8	185.7	98.0
Delaware	482	4.3	241.8	108.8
Ohio	12,303	3.3	228.6	57.2
Connecticut	3,947	1.3	277.5	57.7
Illinois	15,988	3.5	236.2	63.0
Massachusetts	10,524	0.7	298.2	55.7
Pennsylvania	16,789	2.6	240.8	64.1
Rhode Island	2,214	0.5	287.9	66.8
New York	47,819	1.0	322.5	58.1
New Jersey	10,755	0.7	257.8	59.2
Average		2.2	257.7	68.9
Group II				
North Carolina	5,322	9.9	117.3	63.0
California	17,648	8.9	246.9	46.5
Wisconsin	6,979	8.3	235.9	44.6
Indiana	5,408	6.7	217.9	65.6
New Hampshire	1,124	8.3	316.0	61.7
Michigan	9,892	5.9	202.7	42.5
Average		8.0	228.7	54.0
Group III				
Alabama	3,335	15.5	116.8	71.3
Georgia	4,752	12.4	120.3	69.8
Iowa	2,965	19.0	239.4	46.0
Vermont	830	11.5	278.0	45.0
South Carolina	2,137	14.5	118.8	79.1
Virginia	3,644	11.2	156.7	61.2
Minnesota	4,567	18.5	221.0	39.3
Washington	3,412	19.9	223.7	44.8
Kentucky	2,244	18.0	196.2	111.4
Missouri	5,725	12.2	215.1	65.9
Tennessee	3,346	12.6	142.9	37.2
West Virginia	1,602	15.1	146.5	46.9
Average		16.7	181.3	59.8
Group IV				
Arkansas	1,924	27.1	128.1	51.4
Mississippi	1,982	24.0	108.7	70.0
Florida	2,809	20.8	190.1	49.2
Oregon	3,075	31.5	208.9	61.3
Texas	7,129	37.5	142.9	37.2
Oklahoma	1,741	40.2	158.3	41.2
Kansas	1,946	42.3	215.5	53.5
Louisiana	2,389	20.3	168.2	66.8
Maine	1,635	20.3	253.0	55.0
Nebraska	1,344	57.5	181.0	48.1
Colorado	1,602	65.1	201.4	40.0
Average		35.1	177.9	52.2
Group V				
North Dakota	362	192.4	168.2	37.8
Arizona	545	209.0	116.9	28.0
New Mexico	432	281.7	85.4	22.8
Wyoming	256	382.5	135.6	27.9
South Dakota	494	155.9	183.5	36.0
Utah	772	109.9	141.1	37.9
Idaho	664	125.1	158.7	30.4
Nevada	126	877.7	223.6	27.5
Montana	652	225.6	192.0	30.6
Average		284.4	156.1	31.0

a progressive diminution in mortality rate with the decrease in the number of manufacturing establishments.

It is of interest to observe, however, that in some states in each group there is considerable variation in the mortality rates even where the manufacturing establishments are about the same as in the rest of the group. Thus, in group I, Maryland has a relatively low mortality rate from arteriosclerotic heart disease even though the concentration of industry is high. However, the mortality from hypertensive heart disease here is higher than in nearly all states in that group, except Delaware. In group II, North Carolina has a lower mortality rate than in the other states of the group, even though the concentration of industry is approximately the same. In group III, Iowa, Vermont, Minnesota, Washington and Missouri have higher death rates from arteriosclerotic heart disease than do other states of that group, with the concentration of industry per square mile being approximately the same. In group IV, Oregon, Kansas, Maine and Colorado have relatively high mortality rates from arteriosclerotic heart disease, with the concentration of industry no greater than in most other states in this group. In fact, in Colorado the concentration of industry is lowest in this group of states. In group V, Nevada has the highest mortality rate from arteriosclerotic heart disease, with the concentration of industry lowest in this group. Inasmuch as this state has an extremely low population, which according to the 1950 census was only 160,083, its statistical significance is of questionable value. In general, with the few exceptions mentioned above, the close relation between the mortality rates from these diseases and the concentration of manufacturing establishments is definite.

A very interesting observation in this study is that both the mortality rates from these diseases and the concentration of industry have specific geographic distributions. The greatest concentrations of both occur in the northeastern states, particularly the North Atlantic Coast states, as shown in group I. The next highest concentrations, group II, are in adjacent states immediately west and south of the states of group I. California is an exception, being located on the West Coast. The third highest concentrations, group III, occur in those states which in general are adjacent to the group II states, immediately west and south. The exceptions here are Washington which is a West Coast state and Vermont which is an East Coast state. The states in group IV are again in general next to and immediately adjacent to the states of group III in a more westerly and southerly direction. The exceptions are Oregon which is a West Coast state and Maine which is a northeastern coastal state. Group V, which has the lowest concentration of manufacturing establishments and the lowest mortality rates from arteriosclerotic and hypertensive heart diseases, comprised mostly the Western states extending to but not including the three West Coast states. The latter three states, as said before, belong to the other groups.

Discussion

From the observations presented in this paper it will be seen that both the mortality rates from arteriosclerotic and hypertensive heart diseases and the concentration of manufacturing establishments in this country vary markedly in the different states. In general, there is a close parallelism between the concentration of industry and the mortality rates from these diseases in the various states; the greater the concentration of industry in a given state, the higher the mortality rates from these diseases. In some states, however, this relationship does not hold true. The concentration of manufacturing establishments and the corresponding death rates from these diseases show also a specific geographic distribution. The greatest concentration of industry and the highest mortality rates from these diseases are in the northeastern states, particularly the North Atlantic Coast states, and they diminish in fairly direct proportions as we move towards the Southern and Western states. The further west and south we go, the smaller the relative number of manufacturing establishments and the lesser the mortality rates from these diseases. The West Coast states, that is, California, Oregon and Washington, are exceptions.

FACTORS RELATED TO MORTALITY

Diet: We cannot draw any conclusions as to

what may be the possible etiologic factors induced by concentration of industry in given areas which increase the mortality rates from these diseases. We are not justified in assuming that differences in the dietary habits per se in the various parts of the country play a part in the etiology of these diseases. It is hard to believe that dietary habits are directly related to the concentration of industry. We must assume that there are probably a multiplicity of factors induced by an altered mode of living associated with modern industrial life, which predispose to earlier chronic degenerative cardiovascular diseases and death.

Air Contamination: One of the possible factors may be the smog-filled, poisonous air in the industrial regions with its gradual and continuous absorption into the circulation. Another factor might be the confined, indoor life of the factory and office worker with insufficient recreation and activity in fresh open air spaces. Inasmuch as most of the major manufacturing industries are concentrated in and around big cities, the congested city life with its multistory apartment houses and slums further shuts off whatever air and sunshine the worker may get during his off hours. Add to this the great traffic of motor cars and trucks with their exhausts containing carbon monoxide and other noxious gases and we complete the picture of air contamination.

A determination of the carbon monoxide content of blood in city dwellers by Gettler and Mattice[4] and by Hanson and Hastings[5] revealed that about 1 to $1^1/_2$ per cent of hemoglobin is combined with carbon monoxide in various individuals. It was interesting to find that in smokers the percentage ran at times as high as 3 to 4 per cent. Inasmuch as carbon monoxide replaces oxygen from hemoglobin we can readily see how chronic anoxemia may occur over a period of years, predisposing to degenerative changes.

Inasmuch as a frequent outlet for our pent-up emotions is the use of tobacco, the condition is undoubtedly expedited and aggravated by this habit. The effect of tobacco on the cardiovascular system was recently fully summarized by Roth and Shick.[6] To my knowledge no blood studies were made to date of other noxious materials absorbed from contaminated air.

Mechanization of Industry: A third factor that may be operative is the extreme mechanization of industries that converted the worker to a monotonous automaton. Before the industrial revolution in the 19th century every commodity was produced by handpower, requiring individual craftsmanship which gave pride in skills and accomplishments. With the advancement of the industrial revolution the machine has replaced individual craftsmanship, reducing the worker to a mere cog in a wheel. The average worker is deprived of the use of initiative and of fully exercising his talents and originality. What effect this has on his personality makeup and indirectly on his general health must be learned through future investigation.

Increased Tensions: A fourth factor that may be operative is the tremendous speed with which we live. Although mechanization of industry has added greatly to our standard of living and enjoyment, it has also tremendously accelerated our pace. The average person travels more in one week than his ancestors traveled in a lifetime. Whereas it took George Washington about 10 days to travel from Philadelphia to Boston we can now travel that distance in less than one-half hour by jet plane. Our restlessness and lust for speed and travel is so great that even our vacation time is spent in wandering around from place to place. It was estimated that upward of 60 million Americans travel on vacations away from home each year. How much this accelerated speed of travel and general activity may affect our health we are not prepared to tell.

It is very likely that the great tensions of our modern living may affect the autonomic nervous system, altering the hemodynamics of the circulation and thus predisposing to early degenerative changes. A review of the literature dealing with the possible physiochemical, nervous and endocrine changes associated with tensions, as they affect the cardiovascular system, was well summarized in a recent editorial by Russek.[7] An interesting study recently made by Friedman and co-workers[8] revealed that blood cholesterol is increased and blood coagulation is accelerated by occupational stress even when there is no change in the dietary regimen.

One wonders if we had time to accommodate ourselves to the increased momentum and tensions of life within the past 75 years.

That concentration of industry is not the only factor which modifies the mortality rates from arteriosclerotic and hypertensive heart diseases in different states is evidenced by notable exceptions to the usual findings. There are some states such as North Carolina, Georgia, South Carolina, West Virginia and Tennessee where the concentration of industry is high and the mortality rates from these diseases are relatively low. On the other hand, in states such as South Dakota and Montana where the concentration of industry is low, the mortality rates are relatively high. Some of these deviations may perhaps be explained partly by the fact that the concentration of the industries in the given states is localized in small areas of the states, the rest of the areas being free from manufacturing establishments. There must be, however, many other factors which modify the mortality rates, and which require further study.

RELATION TO INCREASE IN POPULATION

The most interesting observations presented in this paper are that the mortality rates from arteriosclerotic and hypertensive heart diseases and the concentration of industry follow a specific pattern corresponding to the migration of the population across the country. In the process of expansion during this country's growth, the part of the country which was first settled, namely the northeastern region, and those regions where the first industrial development took place have the greatest mortality rates from these diseases. As we moved our frontiers westward and southward, the industrial developments and mortality rates followed the same directions. The three West Coast states, California, Oregon, and Washington, however, which underwent earlier and much more rapid development and growth than the other Western states, occupy a position in the higher industrial groups and death rates, as shown by our findings. The increase in population in the decade between 1940 and 1950 alone was 50 per cent for California, 40 per cent for Oregon and 37 per cent for Washington. This tremendous increase in population was associated with the increase in the industrial developments of these states.

SUMMARY

A statistical study was made of the mortality rates from arteriosclerotic and hypertensive heart diseases in the United States in relation to the concentration of manufacturing establishments. It was found that the mortality rates from these diseases as well as the concentration of manufacturing establishments vary greatly in the different states and regions of the country. With few exceptions, there is a definite parallelism between the death rates and the number of manufacturing establishments in the various states. Those states that have the highest concentration of manufacture generally have the highest mortality rates from these diseases. There is also a definite geographic distribution of both the manufacturing establishments and the mortality rates from these diseases, corresponding in location to the sequential expansion of settlements in the various parts of the country since colonial days. In general, those areas which were first settled and where industry was first established have the highest concentration of manufacture and mortality rates.

The observations suggest that there is a multiplicity of factors associated with industrialization which contribute to the etiology of arteriosclerotic and hypertensive heart diseases. Some of the factors may be the smog-filled, poisonous air which we inhale in industrial areas; confined, indoor life; insufficient fresh open air recreation; pent-up emotions associated with monotony of automatic activity of the worker in this machine age; the rapid speed of work and travel in this restless age; and the extreme tensions under which we live.

It is suggested that our future studies of the etiology of these diseases be broader in scope than heretofore, and should include the factors enumerated above. It is my belief that confining our attention only to the study of fat metabolism and dietary habits alone as causes is taking too narrow a view in the investigation of the underlying etiology.

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Cardiac Strain and Trauma

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THE significance of cardiac strain and trauma is assuming increasing importance when we realize that over ten million people are affected with some type of heart disease, and that over 50 per cent of all deaths each year result from this disease.

In defining our terms, cardiac trauma includes: (a) penetrating lesions which may produce hemorrhage, tamponade, pericarditis, contusion and infarction of heart muscle, valvular rupture, embolism, or auricular fibrillation; (b) nonpenetrating indirect injuries, producing cardiac contusion or rupture, or aneurysm formation; (c) strain, producing arrhythmia, valve rupture, myocardial necrosis, and coronary insufficiency patterns. The cause-effect relation between accidents, trauma, industrial stress and ensuing symptoms of cardiac dysfunction constitutes a difficult problem which often involves medical testimony and opinion in legal dispute, both in industrial and nonindustrial situations.

The relation of strain, both physical and mental, to heart disease is of particular importance in industry because of the need for decisions on the capability of an individual to work, his limitations, the liability assumed by the employer, the prognosis of his cardiac condition during employment, the question of aggravation of a minor cardiac disease, and the problems of danger to fellow employes by virtue of sudden change in cardiac function during employment.

Insurance statistics have shown that 80 per cent of workers in industry with a previous coronary occlusion who continue to work live five years, and 60 per cent survive ten years. Among insured men who qualified for total and permanent disability benefits, about half of those with arteriosclerotic heart disease, including those with coronary occlusion, survived 10 years or longer after becoming disabled, and more than a third were living after 15 years.

Because of these considerations, it is important to attempt to evaluate the cause-effect relation of trauma to heart disease so as to better assess contributing factors in a given case, to help evaluate employment possibilities and limitations for work in industry, to aid in determining methods of diagnosis of early or minimal cardiac damage after trauma, and to better prognosticate results of cardiac trauma.

CRITERIA FOR ESTABLISHING CAUSAL RELATION OF TRAUMA TO HEART DISEASE

Physical or Emotional Strain: Sigler[1] has pointed out that moderate strain followed by continuous symptoms of cardiac dysfunction constitute criteria for causal relationship. He noted that acute coronary insufficiency secondary to emotional or physical strain could lead to myocardial necrosis, but emphasized that the sequence of effort or strain followed by continuous symptoms with the appearance of laboratory confirmatory changes within a reasonable period was a necessity. In the presence of no prior heart disease, this sequence was sufficient, while in the presence of pre-existing disease, acute cardiac changes of a recent nature must be demonstrable.

In a later publication, Sigler[2] stated that "myocardial ischemia, ischemic necrosis, and infarction, which are the underlying causes of the clinical manifestations of the acute phase of coronary artery disease, are not due solely to coronary thrombosis. They may result from other acute occlusive processes or from acute functional disparity between the demand and the supply of the blood to the heart muscle. Emotional and/or physical strain are potent factors in the production of the acute phase of

the disease. . . . The strain must not necessarily be unusual provided it is great enough and has been undertaken at a vulnerable phase of the disease. The symptoms following the strain must not necessarily be severe soon after, but must be continuous and followed within a reasonable time by evidence of structural myocardial damage. If there was pre-existing cardiac disease, evidence of fresh myocardial injury must be demonstrable soon after the strain. Physically non-strenuous work if performed under emotional excitement or upset may precipitate an attack. Death may occur soon after a given strain, and in the absence of demonstrable acute coronary occlusion at autopsy, is to be attributable to an acute myocardial ischemia due to functional coronary insufficiency especially where coronary atheromatosis is marked. Delayed death of several years following an acute cardiac insult may be due to such insult if autopsy findings reveal an extension at the original site of injury, and there are no other acute pathologic findings to account for death."

Weiss[3] and others have shown that many physiologic changes occur with emotional stress and strain such as changes in pulse rate, blood pressure, cardiac output, clotting time, blood viscosity and adrenalin output, arrhythmia, increase in permeability of pulmonary capillaries, and rises in serum cholesterol. Studies of patients suffering from coronary occlusions have shown an incidence of 49 per cent with preceding tension of a gradually increasing nature. Tension may also be present in sleep, as exemplified by teeth grinding, nightmares, etc., so that the occurrence of cardiac dysfunction while at apparent rest does not invalidate the concept of preceding tension or an acute emotional stress precipitating cardiac damage. This may occur in conjunction with an accident of minor extent otherwise, or in association with emotional stress while at a work not physically involving unusual exertion.

Cardiac Trauma: Taylor[4] reviewed 350 cases of heart damage secondary to nonpenetrating trauma reported up to 1953 and stated that 15 per cent developed arrhythmias and two-thirds of these developed permanent changes. Arenberg,[5] in analyzing 28 cases of traumatic heart disease, found no relation between the severity of thoracic injury and the incidence of cardiac injury—he felt that cardiac injury was a function of the resiliency of the chest wall and the force of the blow. Sprague[6] emphasized that the results of any type of injury will vary with the etiology of the underlying type of disease, i.e., strain may rupture an aneurysm while the same strain in the presence of rheumatic mitral disease may result in auricular fibrillation. He pointed out that remote trauma may rupture heart valves or chordae by muscular effort, may reactivate rheumatic fever, may result in arrhythmias, or may, by direct irritation such as from inhaling fumes or gases, result in myocardial necrosis with arrhythmia. He cited the following criteria for providing relation between trauma and heart symptoms and stated that at least one must be present: (a) electrocardiographic changes, (b) unexplained acute enlargement of the heart, (c) abnormal rhythm, (d) pericardial rub or evidence of tamponade, (e) aortic diastolic or mitral systolic murmur with signs of failure, (f) heart failure immediately following trauma or strain, (g) immediate onset of angina, or onset of occlusion in 24 to 48 hours. Osborn[7] explained the development of arrhythmias following compressive chest trauma as the result of contusion of the right auricle extending to the sinoauricular and auriculoventricular nodes.

Moritz[12] in analyzing the pathologic changes following trauma and stress has indicated that direct trauma may produce cardiac shock with ventricular asystole or fibrillation, cardiac contusion, laceration, valve rupture, or coronary artery contusion with posttraumatic shock resulting in hypotension, coronary ischemia and nonthrombotic infarction. He explained the effects of indirect trauma such as stress as being due to physiologic changes of pulse and blood pressure with development of relative coronary insufficiency or hemorrhage into atheromatous plaques with swelling and lumen obstruction.

Effort and Coronary Insufficiency: In assessing the role of effort, Yater[8] reported on 950 autopsy cases of all forms of coronary sclerosis in the Armed Forces, and in the younger age group the terminal cardiac episode occurred during strenuous activity in 32 per cent. French

and Dock,[9] in a similar study, found a similar correlation between activity and terminal episodes.

Sigler, in numerous publications, has indicated his belief that death with coronary disease may be sudden without pathologic findings as a result of ventricular fibrillation or asystole, or heart failure. In each instance these are precipitated by a period of acute myocardial ischemia which has followed physical or mental strain in the presence of an abnormal coronary circulation. Master[10] was of the opinion that occlusion is rarely the result of strain, but that protracted episodes of coronary insufficiency are common pathogenic factors. He stated that the history should show subjective distress resulting from physical or mental stress persisting for 30 minutes or more, or recurring several times. He indicated that coronary insufficiency was as common as occlusion, and in 100 cases found a relation to strain in one-third to one-half. He also was of the opinion that occlusion occurred after effort in only 2 per cent of cases because of the time needed for a thrombus to form, and effort merely makes the collateral circulation inadequate in the presence of partial obstruction. According to Master[10] this is borne out by the finding of an organizing thrombus in 38 per cent of cases of fatal coronary occlusion associated with effort as compared to 11 per cent of those in which patients died in bed.

Kapp,[11] in a review of 42 cases of coronary thrombosis following trauma or effort, stated that possible mechanisms included intimal rupture and hemorrhage, formation of intramural hematoma, changes in viscosity and permeability during stress, and release of atheromatous material to form a clot.

Summary of Criteria of Cardiac Disability Due to Strain: In evaluating the criteria whereby strain induces cardiac disability, it is apparent that severe strain may be followed by signs of cardiac insult, and that this strain need not be unusual if the patient has already reached a vulnerable phase of coronary disease. The symptoms following strain should be continuous and followed in a reasonable period by the development of laboratory or clinical evidence of damage. Death from coronary disease may be sudden without pathologic findings and may be due to ventricular fibrillation or asystole, or heart failure—the precipitating cause is acute myocardial ischemia, which has followed physical or mental strain in the presence of advanced coronary disease.

Occupation and Coronary Attacks: Although occupation is not causally related to the development of coronary heart disease, certain fields of endeavor show a predilection. Studies of series of patients in varied occupations have revealed a greater incidence among people in managerial or skilled labor fields. These same studies have shown an increased incidence of occurrence in younger patients in cool weather, in late afternoon when activity was at its highest peak, and usually with premonitory symptoms.

Medicolegal Problems in Cardiac Trauma

A paradox exists in legal decisions on heart disease secondary to stress and exertion, with many medical experts disagreeing. A study[13] initiated by the Cardiacs in Industry Committee of the California Heart Association revealed that when five expert physicians analyzed 319 cases, only 14 per cent were in unanimous agreement, and when the same case was analyzed a second time by the same physician, only 80 per cent confirmed the first opinion they had rendered. When compared to the awards of the Industrial Accident Commission, there was roughly a 70 per cent correlation. In cases involving unusual exertion, the awards were made in almost 90 per cent of cases. Two-thirds of the cases of heart disease were reported in occupations classed as moderate or mild exertion, and 50 per cent of the patients were under the age of 55. In California, statutes of the labor code, in effect, establish the presumption that in any case of heart disease arising from police or firemen's activities during hours of employment, a causal relation exists.

The courts have ruled that an employe is entitled to compensation whenever his condition is aggravated by the employment, or if the employment hastened death or disability. The question of whether the employment precipitated the collapse of a diseased heart prior to the time when the normal progress of the disease would have brought on such a collapse is one

of fact. The court also stated: "Whether the strain is a usual or unusual one is only one of the facts involved. If there was a strain usual to that type of employment, the injury or death is compensable if there is competent substantial evidence to show the causal connection between that strain and the collapse." Arenberg,[14] in a study of 250 cases of nonpenetrating chest injuries, felt that the majority of cases of cardiac damage were not recognized or diagnosed.

Diagnosis of Cardiac Trauma

Having considered the evidence for relation between effort and heart damage, and the mechanisms by which this may operate, let us now briefly review the modes of diagnosis of cardiac trauma. Many authors emphasize the value of electrocardiographic changes,[15] particularly in acute situations. Of course, the pattern of the symptoms and/or findings of cardiac enlargement, murmurs, rubs, signs of heart failure, and presence of abnormal rhythms are frequently of significance. Among the laboratory modalities available, tests showing changes in serum enzymes have recently become popular in the diagnosis of cardiac disease, particularly on an acute basis.

Serum Transaminase: A recent study[16] of the relation between serum glutamic oxalacetic transaminase in conditions associated with myocardial infarction revealed that elevation of the SGO-T activity was present in a large percentage of patients after bodily trauma, but this was not specific for cardiac damage. In that study, of the 72 per cent of patients showing elevation, only about one-fourth had demonstrable cardiac damage. Chinsky[17] has described an elevation as unusual in trauma without considerable muscle necrosis or liver damage, and has indicated that infarction of as little as 10 per cent of the total myocardium would give rise to an elevation. He also pointed out a few instances of a rise in the enzyme level associated with an arrhythmia alone. MacDonald *et al.*[18] have studied the level of serum lactic dehydrogenase in myocardial disease and found the technique to be simpler and the changes of longer duration (up to six to eight days). In addition, the level tends to vary significantly between acute ischemia and actual infarction, thus helping to separate these entities when the electrocardiogram is indefinite. Studies on the serum glutamic pyruvic transaminase suggest that this is more helpful in liver disease than cardiac dysfunction.

LaDue[19] has pointed out that rises in serum glutamic transaminase occur after skeletal muscle trauma, and may persist four to seven days. He also indicated that trauma to skeletal muscles during surgery is followed by minimal to moderate increase in SGO-T, SGP-T, and SLD activity for one to six days, and this is also true of mechanical injury to skeletal muscle.

C-Reactive Protein: The C-reactive protein has been reported to be almost universally positive after the third day in acute transmural infarction, but tends to be negative in coronary insufficiency without infarction. The test may be useful when the patient is first seen and tested more than four days after the suspected cardiac trauma, since, in this instance, the enzyme tests will tend to be negative. A change in C-reactive protein from positive to negative can be expected after two to three weeks in the presence of cardiac damage, so this may more reliably indicate the course of the disease than the sedimentation rate, which tends to be elevated for long periods despite the absence of other signs of active disease.

Illustrative Case Histories

To illustrate some of the problems involved in assessing the relationship between effort and subsequent cardiac damage, several case histories seen by me for the Industrial Accident Commission have been abstracted from the medicolegal files.

Case 1. *Acute Coronary Insufficiency Associated with Physical Strain:* A 55-year-old carpenter, who had been employed as a general carpenter for the past ten years, was given the task of lifting long sections of 2 x 4 planks and carrying them up a stairway. While engaged in this function, he complained of heaviness and pressure in the chest area. He continued to work, however, for three hours. At this time, the chest discomfort became more severe, nausea and excessive sweating appeared, and he died twenty minutes later. No prior history of heart disease was obtained, nor were any chest symptoms present prior to the day of his demise. A physical check-up one year before had not shown any physical abnormalities, but his electro-

cardiogram at the time of his check-up examination had revealed low T waves in lead 1, aVL, V_5 and V_6 (interpreted as showing nonspecific myocardial damage).

Postmortem examination revealed an enlarged heart weighing 400 g with considerable narrowing and sclerosis of the coronary vessels, thickening of the myocardium, and areas of fibrosis of the myocardium.

Medicolegal interpretation was that of acute coronary insufficiency as a result of unusual effort in the presence of an already inadequate coronary circulation.

Comment: Death in this case was ascribed to acute coronary insufficiency in an already diseased heart. Unusual effort or strain, followed by persistent chest pain, together with autopsy findings of no recent myocardial infarction or coronary occlusion, is a well-recognized physiologic phenomena. When the insufficiency is prolonged sufficiently, acute myocardial necrosis may follow. The industrial law in California provides that when death can be shown to be due to industrial effort, a full award is made regardless of pre-existing heart disease.

CASE 2. *Myocardial Infarction Secondary to Chest Trauma:* A 62-year-old construction worker was struck in the mid-chest area by a swinging steel beam suspended from a crane. He was knocked to the ground, and complained of throbbing discomfort in the chest area together with shortness of breath for over an hour. Later in the day, he felt better and continued at light work. That evening, he awoke twice with dull chest aching, which persisted for several hours. He worked at a lighter job the next day, but on the way home developed severe chest pain with profuse sweating. A physician was summoned, hospitalization was recommended, and electrocardiograms were taken. Electrocardiogram on admission showed deep Q waves and elevated ST segments in leads 2 and 3 together with depression of ST in leads 1 and V_5. C-reactive protein was three plus and serum transaminase was 94 (normal below 50). A diagnosis of acute posterior myocardial infarction was made, and anticoagulants begun.

There was no prior history of heart disease, but his wife stated that he had had frequent episodes of upper abdominal distress after meals or with considerable walking, relieved by sitting still for a few minutes.

Comment: While trauma will rarely cause coronary occlusion with myocardial infarction in a normal heart, the history of some discomfort with heavy meals or walking, relieved by rest, indicated pre-existing coronary artery disease. Following the acute trauma, chest distress appeared intermittently for the next 36 hours. Electrocardiographic and laboratory findings confirmed the diagnosis of acute occlusion with infarction. The time interval was consistent with that required to develop a thrombosis, and the medicolegal interpretation was that of trauma inducing heart damage.

CASE 3. *Acute Coronary Insufficiency Due to Emotional Stress:* During the course of employment as a maintenance man, a 59-year-old Negro male became involved in a violent quarrel with the foreman. The argument persisted off and on for almost an hour. Near the end of the argument, the maintenance man developed an acute pressing pain in the chest area, began sweating profusely, and had to be helped to a nearby sofa. The pain gradually receded, but he was unable to continue working, and went home several hours later with dull chest discomfort still present. A physician was summoned and an electrocardiogram taken without finding any abnormality. A repeat tracing the following day was still within normal limits, but serum transaminase was elevated to 75 and a low-grade fever was noted. Two days later, T wave inversion in leads 1, aVL, V_5 and V_6 was noted, and the transaminase was still elevated to 64 while the C-reactive protein was two plus. He was kept in bed for two weeks, and gradually improved with the use of vasodilators and daily subcutaneous concentrated heparin.

Review of his history revealed a chronic hypertension averaging 165/105 for several years, and the presence of occasional exertional dyspnea. No previous electrocardiograms were available for comparison.

Comment: In the presence of chronic diastolic hypertension and symptoms of dyspnea, preexisting heart disease was presumed to have been present. An episode of acute coronary insufficiency was precipitated during a violent quarrel, and myocardial necrosis subsequently developed. The time sequence was such that a coincidental heart attack was unlikely. The lag in development of electrocardiographic changes might have confused the picture, but the laboratory data proved helpful in evaluation. An award was made on the basis of industrial trauma precipitating cardiac damage.

CASE 4. *Acute Coronary Occlusion Not Due to Strain:* A 47-year-old white male janitor complained of right chest pain during the course of sweeping, and had to stop working several times for a few minutes during the day. This recurrent chest pain persisted for one day, but each episode was transient in nature. He stopped working for five days' vacation, and on the morning of the fifth day awakened with severe, pressing chest pain which persisted for several hours. Electrocardiogram taken at that time revealed elevated ST segments in leads 2, 3 and aVF with slight depression in lead 1. No Q waves were noted. Serum transaminase was elevated to 95. The following day, deep Q waves

appeared in leads 2, 3, and aVF and early T wave inversion was noted. Pain had subsided but he was kept at bed rest, and a diagnosis of acute posterior myocardial infarction was made.

Past history revealed no prior heart disease, heart symptoms, or the presence of hypertension or diabetes. Work history revealed no unusual physical or emotional strain. A physical check-up six months before had been normal, as was the electrocardiogram at that time.

Comment: Although it was argued that an episode of coronary insufficiency during work had precipitated the subsequent coronary occlusion, we felt that the hypothesis was not tenable in this case. The chest pain initially was poorly localized, and did not persist; no unusual exertion preceded the pain, and no pre-existing heart disease was known to be present; there was no pain during the five days of vacation, and the acute episode began on the fifth day, terminating in an acute occlusion with electrocardiographic changes of only a relatively short duration. No award was made for industrial trauma causing heart damage.

CASE 5. *Acute Myocardial Infarction Associated with Unusual Work:* A 68-year-old carpenter, who had been doing part-time light carpentry, began working full-time building stages on a moving-picture set. The work involved lifting heavy planks, carrying them several hundred feet, removing rusty nails with one hand while bracing the planks with the other hand, and then piling them on a stack of lumber about 3 feet high. He complained of chest discomfort after several hours on the second day of work. After resting, he worked intermittently the rest of the day, but in the late afternoon, developed very severe, crushing chest pain together with profuse sweating and slight dyspnea. The chest pain was still present during the evening at home, and the family physician was called. He administered an opiate after noting findings of a rapid, irregular heart beat, sweating, basal lung rales, and evidence of generalized sclerosis. Blood pressure was 105/70 at the time of his examination. The patient died around midnight, but no postmortem examination could be obtained.

Past history revealed the presence of long-standing coronary heart disease with mild chronic angina, and two prior episodes of cardiac decompensation. No prior occlusions had occurred. Mild hypertension had been present for four years averaging 150/100.

Comment: The final diagnosis in this case was acute coronary insufficiency with myocardial necrosis secondary to chronic arteriosclerotic heart disease with angina pectoris. The pattern of severe, continuous chest pain associated temporally with heavy, unusual work culminating in death, made this diagnosis and the relationship between industrial effort and cardiac damage entirely consistent. While it was argued that moderately severe pre-existing disease at this age would have predisposed this worker to a coincidental heart attack through the natural development of coronary heart disease, this episode was considered to be the direct result of effort. It is well-recognized that less effort will be required to produce cardiac damage in a heart with extensive coronary disease than in one with minimal prior disease. The mechanism of death in this case was similar to that of case 1.

SUMMARY

(1) The importance of an accurate and careful appraisal of cause-effect relationship in cardiac trauma, both direct and indirect, has been emphasized.

(2) The physiologic and clinical description of the pathogenesis of cardiac damage, secondary to trauma and strain, has been reviewed.

(3) Evidence indicates that trauma and strain may be considered significant if associated in a temporal sequence with clinical and/or laboratory evidence of cardiac damage.

(4) Varied criteria of diagnosis of early or minimal cardiac changes have been reviewed, including electrocardiographic patterns, changes in serum enzymes, and clinical abnormalities.

(5) Illustrative case histories are included to demonstrate the application of these criteria in an evaluation of effort or strain in relation to cardiac damage.

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Coronary Heart Disease

III. Chronic Arrhythmias as Influenced by the Beck Operation*

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MORE THAN 350 patients with coronary heart disease were operated on by Dr. Claude S. Beck in Cleveland in the six years covered by this study. The diagnosis of coronary heart disease had been established prior to operation on the basis of existing criteria.[1,2] (Another 200 patients referred for operation were rejected because the diagnosis could not be established, or because other organic disease simulating coronary heart disease was found.)

Of profound importance is a unique experience not heretofore available, in patients with coronary heart disease, for direct observations on such hearts. These observations included direct electrocardiographic recording from various epicardial, intramyocardial, and endocardial areas, and extensive hemodynamic studies, including measurements of coronary blood flow and myocardial utilization of oxygen and various substrates. Thus, we have availed ourselves of a remarkable opportunity for a direct correlation of clinical, experimental, surgical, and pathologic observations.

Its very nature is such that clinical observation is the *sine qua non* in evaluating the treatment of coronary heart disease. But this disease continues to defy "objective" evaluation. Consequently, its treatment has suffered from a great reluctance to make the necessary correlations between clinical and experimental observations. The historical development of present-day comprehension of coronary heart disease is characterized by a disposition to marvel at, and then reject, reproducible and significant clinical observations, rather than to suffer the inconvenience of adapting "well-established" concepts to apparently mutually exclusive observations. As a matter of fact, there exists a general resistance toward positive action under any circumstances. The natural reluctance of the physician to transfer laboratory results to the patient has reached its greatest peak of development in the field of coronary heart disease.

Obvious clinical benefit associated with procedures which have adequate laboratory substantiation should not be categorically rejected merely because human coronary heart disease cannot be reproduced exactly in the laboratory, or because its unpredictability defies simple statistical evaluation. Indeed, if need be, it is possible to achieve "progress without statistics."[3]

Even now, during the observation of the tercentenary of William Harvey's death, many of the significant contributions made since his time are still engulfed in controversy. Furthermore, unless there is adequate reappraisal of certain outmoded concepts, such controversy will always be encouraged by seemingly paradoxical but impressive clinical benefits associated with such dissimilar agents as nitroglycerin and surgical operation for coronary heart disease. Neither of these presumes to produce tremendous alterations in total coronary inflow, but their admittedly limited contributions are critically decisive in the precariously compensated circulation of a potentially ischemic area.

METHOD OF STUDY AND CLINICAL OBSERVATIONS

Of 350 patients operated upon, in addition to angina pectoris a persistent arrhythmia was a

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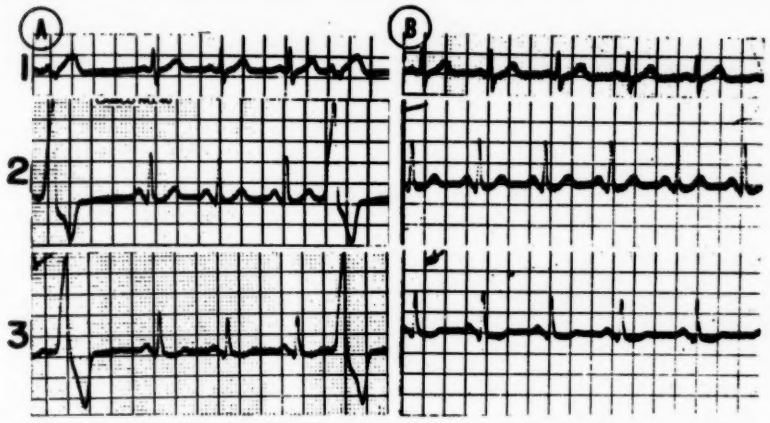

Fig. 1. (A) Ventricular extrasystoles at rest in a patient with coronary heart disease prior to operation. (B) One year after operation extrasystoles are abolished. (ECG leads 1, 2, 3 shown.)

prominent feature in approximately 8 per cent. As a matter of fact, in 9 patients symptoms relating to the arrhythmia were of more concern to the patient than was angina pectoris. This report is primarily concerned with a series of 20 patients in whom significant arrhythmias were exhibited prior to operation, and in whom long-term observation has permitted "objective" evaluation of the patient's present status.* In these 20 patients, prior to operation, ventricular extrasystoles were prominent in 15 (Figs. 1 and 2), auricular extrasystoles in 3 (Figs. 3 and 4), and sinus tachycardia in 2 (Fig. 5). Generally, the arrhythmia could be detected at rest, and exercise caused an increase in frequency. However, in 4 of these patients (3 with ventricular and 1 with auricular extrasystoles), only rare extrasystoles were present at rest, but invariably exercise or emotional stress resulted in marked intensification of the arrhythmia (see Figs. 2 and 4).

Sinus Tachycardia: Persistent sinus tachycardia (heart rate over 100 per minute) was present at rest in 2 patients (both women). In both of these, the chronic tachycardia had been initiated following an acute myocardial infarction, one to two years prior to operation. In neither was there evidence of hyperthyroidism. Uptake of I^{131} was normal in each.

In one patient (see Fig. 5), the heart rate was constantly observed to be more than 115 per minute, and

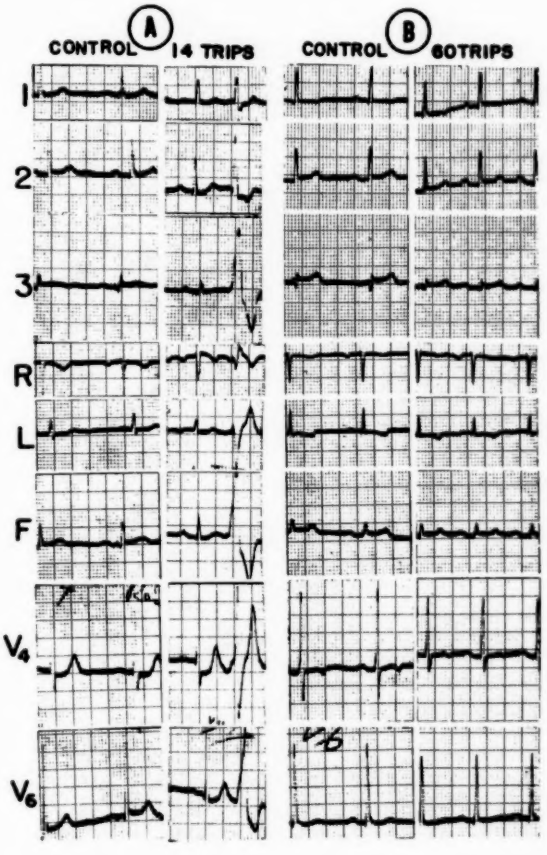

Fig. 2. (A) Essentially normal control ECG prior to operation; with exercise (14 trips), S-T segment deviation and frequent ventricular extrasystoles were associated with anginal pain which precluded further exercise. (B) Nine months after operation even after 60 trips, there was no significant change in the ECG from the control. (ECG leads as indicated.)

* Generally speaking, the usual drugs had little or no effect upon these arrhythmias.

Fig. 3. (A) Auricular extrasystoles occurring at rest prior to operation. (B) One year after operation, no extrasystoles detected. (ECG lead 2.)

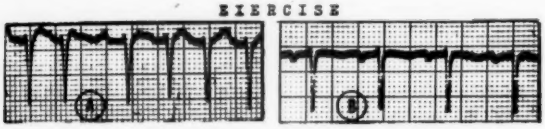

Fig. 4. (A) Auricular extrasystoles, infrequent at rest, markedly increased following exercise, with runs of auricular tachycardia prior to operation. (B) Two years postoperatively, even after protracted exercise, no extrasystoles detected. (ECG lead V_1.)

full digitalization had no influence upon it. The slightest physical activity touched off an immediate increase in heart rate to 140–160 per minute, so that the patient was more or less completely incapacitated by this tachycardia (with only moderate pain). Although this patient presented an almost prohibitive risk, operation was undertaken reluctantly, as a last resort. After induction of anesthesia, a heart rate of 115 persisted. Remarkably enough, she tolerated the operative procedure quite well; there was no undue irritability even during abrasion. Near the end of the operation, it was noted that the heart rate was below 100 per minute, at which level it was maintained for the immediate postoperative period.

On the second postoperative day the heart rate had fallen to 96 per minute and continued to decrease, so that at the time of her discharge 14 days postoperative a heart rate of 75 per minute had been consistently observed. During the early months after operation, concomitant with her dramatic clinical improvement, normal rate and rhythm have persisted (see Fig. 5).

The course of events in the other woman with sustained sinus tachycardia was quite similar; two years after operation she also now exhibits normal sinus rhythm without tachycardia at rest and only occasional symptoms of coronary insufficiency on exertion.

Relation Between Arrhythmia and Coronary Insufficiency: All the patients in this series demonstrated a definite relationship between the chronic arrhythmia and other manifestations of coronary heart disease. Usually, an acute myocardial infarction preceded the onset of the arrhythmia. During attacks of angina in these patients the arrhythmia generally became more pronounced and then diminished as the attack subsided. In one patient, awareness of extrasystoles served as a precursor of an impending anginal attack, so that by taking nitroglycerin the patient could frequently abort the attack.

That these arrhythmias are a manifestation of coronary insufficiency is attested to by their frequent appearance following exercise or emotional stress and by their usual association with angina. As a matter of fact, the appearance of an arrhythmia during an exercise tolerance test represents confirmatory "objective" evidence of coronary heart disease.

A case in point is that of a 41-year-old male who suffered a myocardial infarction one year prior to operation. Soon thereafter, on returning to his previous occupation as a lathe operator, he became aware of frequent skipped beats (ventricular extrasystoles), particularly under stress. These recurred so frequently, despite all medication, that he was completely incapacitated by this alarming symptom and its attendant aura of impending doom (see Fig. 1).

Generally, he had little pain during these attacks; the extrasystoles comprised an anginal equivalent. Nitroglycerin significantly reduced the extrasystoles, but only temporarily. Operation was performed on April 29, 1953. On the day prior to operation, he received 1.2 mg digitoxin orally in divided doses. Although ventricular extrasystoles occurred throughout the operation, epicardial abrasion was well tolerated and there were no alarming periods of arrhythmia (Fig. 6).

On the first postoperative day an occasional ventricular extrasystole could be detected. At the time he was

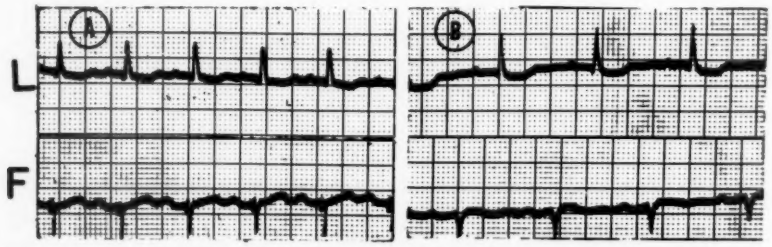

Fig. 5. (A) Sinus tachycardia, with a ventricular rate consistently higher than 110/minute prior to operation. (B) Two weeks after operation, decrease in heart rate which continues below 100/min at rest to present, 2 years postoperatively. (ECG leads aVL and aVF shown.)

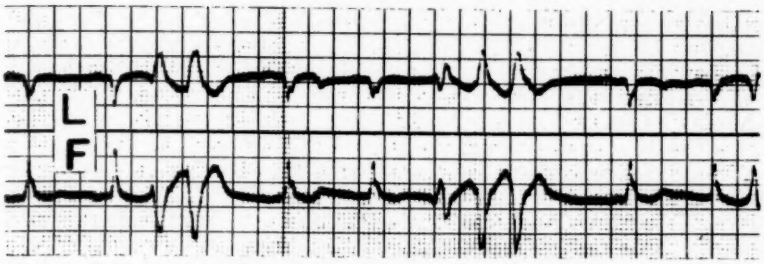

Fig. 6. Ventricular extrasystoles recorded during epicardial abrasion at operation. (ECG leads aVL and aVF shown.)

discharged from the hospital no extrasystoles were detected, and the patient himself felt tremendously relieved. During the first two years following operation extrasystoles occurred on occasion, and then only during extremes of physical or mental activity. About two and one-half years after operation, for a period of about one week the extrasystoles recurred with alarming frequency. He was hospitalized for six days. There was no evidence of recent myocardial damage, and he returned to work after a four-week absence. Since that time he has been completely asymptomatic; no ventricular extrasystoles have been detected, and he has not missed a day's work in the past year.

Effect of Surgery on Arrhythmias: Among patients being evaluated as candidates for coronary heart surgery, chronic arrhythmias are found much more frequently in those who are eventually rejected than in those accepted for operation. Although the arrhythmia per se does not constitute a contraindication, generally those patients also have congestive heart failure, severe hypertension, or concomitant valvular disease. Only rarely has a patient with auricular fibrillation proved to be an acceptable candidate for operation.

It should be noted that the 20 patients in this series represent a select group in that this is a retrograde study of patients who are alive at present, without reference to others who may have died during this period. The follow-up period ranges from a minimum of one year to a maximum of six years.

In many instances, within 24 hours after operation an apparent diminution in extrasystoles had already occurred. In approximately one-half the cases the arrhythmia had been completely abolished within the first week after operation and subsequently there was only an occasional transient recurrence, usually associated with clinical episodes of coronary insufficiency.

Generally speaking, the improvement in the arrhythmia more or less paralleled the patient's clinical course. In 3 of the 15 patients with ventricular extrasystoles, in each case associated with extensive muscle damage, there has been little apparent alteration of the previous symptoms; by the same token, these patients have continued to exhibit the same degree of arrhythmia as before. In 17 of the 20 patients ultimately there was either complete abolition or at least a marked diminution of the arrhythmia. This was associated with improvement in the patient's clinical status in each case.

Observations on the Behavior of the Heart During Surgery, with Special Reference to the Influence of Digitalis

Preoperative Digitalization: In all patients undergoing operation for coronary heart disease, complete digitalization is carried out prior to surgery. This is done even in the absence of congestive failure or specific arrhythmias. After operation, digitalis is continued until the patient is discharged from the hospital; however, in patients with extensive damage and cardiac enlargement, long-term maintenance is encouraged. Although contrary to the recommendations of most cardiac consultants, early in this work it became evident that digitalis had no deleterious influence and, in fact, contributed to the maintenance of greater stability during operation. This observation was further strengthened during resuscitation experiments in the dog laboratory: Digitalized dogs could be resuscitated more readily and more frequently than those not digitalized, and these dogs demonstrated greater resistance to reversion to ventricular fibrillation.

On the basis of present concepts, both digitalis and coronary insufficiency would tend to in-

crease the irritability of the heart, so that it might well be anticipated that the simultaneous action of both factors would predispose such hearts to serious arrhythmias, particularly when subjected to the mechanical trauma of operation. Theoretical concepts to the contrary notwithstanding, digitalis *diminishes* the dangers associated with arrhythmias. The various ventricular and supraventricular arrhythmias, which had been an almost invariable accompaniment to the operative procedure, have been significantly decreased by adequate digitalization.

Of particular significance is the observation that the ischemic heart, heretofore considered hyperirritable and prone to fatal arrhythmias induced by relatively insignificant trauma, tolerates the trauma of operation and epicardial abrasion remarkably well. Such an observation should help dispel many ancient fears concerning the tolerance of such patients for various procedures which are necessary for their well-being. Certainly, if major surgery is indicated in such patients, it should not be withheld, or performed only as a last resort, merely because the patient has coronary heart disease.

Bradycardia and Hypotension During Surgery: During operation, especially soon after induction of anesthesia, moderate bradycardia and hypotension may occur. Small doses of atropine sulfate (0.2 mg intravenously) specifically prevent a potentially dangerous slowing of the heart. Whenever moderate hypotension occurs, a rest period is observed and the lungs are well inflated. A small dose of atropine may then be tried. If hypotension persists, a gentle vasopressor (mephentermine, 7.5 to 15 mg intravenously) is given. Frequently this produces a sustained rise in pressure, although occasionally repeated doses are required. Rarely a more potent vasopressor drug (norepinephrine) is required. Generally, there is remarkably little fluctuation of blood pressure during the operation.

Arrhythmias During and After Surgery: During cardiac manipulation, various ectopic beats occur. Especially during epicardial abrasion, frequent ventricular premature beats and even runs of ventricular tachycardia appear, but subside immediately when abrasion ceases (see Fig. 6). Only rarely do these ectopic beats persist. There has been no instance of persistent ventricular tachycardia or fibrillation associated with this manipulation. So-called antifibrillatory drugs are not used routinely. Procaine amide or quinidine should not be used empirically, in view of the myocardial depression produced. Only rarely is it necessary to use even small amounts of procaine amide for a particularly irritable heart.

In the early postoperative period, a variety of benign and serious arrhythmias may occur. Previously, a frequent and most alarming arrhythmia was auricular flutter, usually with a 2:1 A-V block. The preoperative use of digitalis has completely eradicated this complication.

Digitalis, Extrasystoles, and Cardiac Efficiency: In the presence of ventricular extrasystoles, unless this arrhythmia is caused by digitalis, there is no good evidence that digitalis administration is contraindicated (for fear of encouraging the arrhythmia). As a matter of fact, by increasing cardiac efficiency, digitalis may well abolish these extrasystoles. Even in the absence of overt heart failure, digitalis improves myocardial contractility. Of profound significance is the observation that both the Beck operation[1] and digitalization give ballistocardiographic evidence of improved contractility in patients with coronary heart disease (Fig. 7). The improvement following digitalization, with a pattern resembling that following operation, further emphasizes the reversible nature of the impaired myocardial contractility in coronary heart disease.[4]

In summary, then, digitalis appears to have a specific beneficial inotropic and chronotropic influence on such hearts in patients with coronary heart disease undergoing the Beck operation. Laboratory and clinical evidence indicates that digitalis (1) *decreases* the irritability of the heart, particularly during epicardial abrasion; (2) *decreases* incidence of various supraventricular arrhythmias occurring during induction and maintenance of anesthesia; (3) appears to aid in maintaining normal stroke volume and heart rate during operation; and (4) increases the ease of resuscitation of dogs (and no doubt of human beings) following cardiac arrest.

Discussion

Arrhythmias, Coronary Flow, and Myocardial Ischemia: In addition to the alarming symptoms

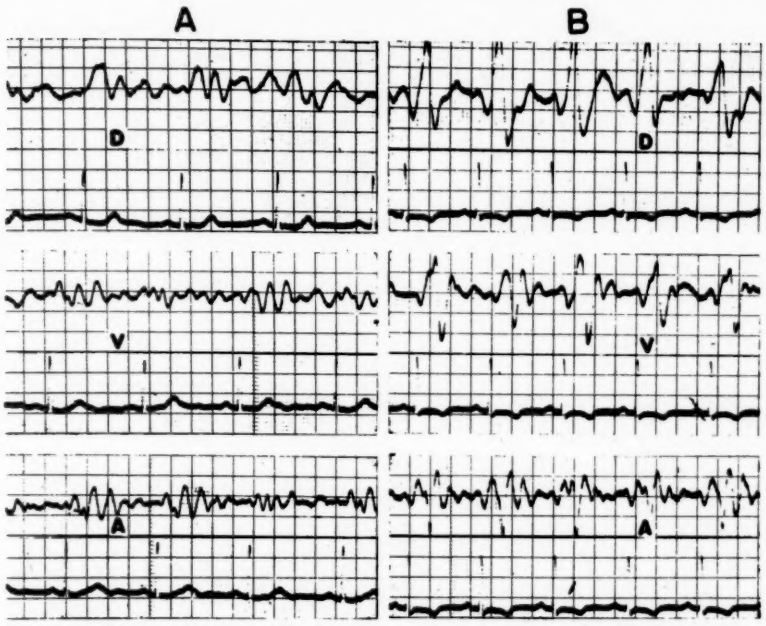

Fig. 7. Ballistocardiogram (displacement, velocity, and acceleration) preoperatively; (A) before digitalization; (B) after digitalization, showing marked improvement.

and the sense of impending doom associated with chronic arrhythmias, in the precariously compensated circulation of coronary heart disease even an occasional extrasystole might further compromise coronary blood flow and thus, per se, have a deleterious effect. In a patient with coronary heart disease, any tachycardia may have disastrous consequences. As the rate increases above a given critical level, not only is heart work increased without a corresponding increase in coronary blood flow, but also coronary flow may show even an absolute *decrease* as diastolic flow is compromised by the increased rate.

It has long been known that experimental coronary artery occlusion gives rise to acute arrhythmias.[5,6] In the course of acute myocardial infarction, arrhythmias are quite common, and they may be of grave prognostic significance.[7–10] Usually they appear within the first few days following infarction and are generally transient. Persistent sinus tachycardia is considered an ominous prognostic sign, particularly since it is so frequently an indication of extensive muscle destruction.

Atrial extrasystoles are frequently a consequence of a compromised blood supply to the atrium. Experimental ligation of the right coronary artery frequently results in arrhythmias ranging from sinus arrest to atrial extrasystoles and atrial tachycardia, as well as in producing posterior ventricular infarction.

Ventricular extrasystoles are present in about 5 per cent of patients with coronary heart disease without myocardial infarction and may appear as the first sign of the disease.[8] The appearance of these extrasystoles with exercise is particularly significant, since in the normal individual, exercise usually abolishes them.

In many patients with coronary heart disease these arrhythmias are a manifestation of myocardial ischemia; the increased irritability of areas of the myocardium results in ectopic foci which intermittently fire prematurely. It can be shown that these ectopic foci are located not within an area of ischemia but at the boundary between ischemic and relatively nonischemic myocardium.[11–13] In patients with coronary heart disease these ectopic beats are thus an expression of the "electric instability" of such hearts and may well be an early manifestation or precursor of the ultimate fate of the patient; that is, mechanism death due to ventricular fibrillation. The great majority of deaths associated

with coronary heart disease are related to this bioelectric phenomenon.[13]

Ventricular Fibrillation and Mechanism Death: It can be shown that ventricular fibrillation following coronary artery ligation is introduced by an accelerating series of premature beats.[11,12] These ectopic discharges originate at the transitional zone and usually are followed by ventricular fibrillation within 10 minutes after artery occlusion.

An ischemic area of myocardium has a marked decrease in fibrillation threshold.[14–16] Within a very thin sheet of boundary cells between ischemic and nonischemic muscle there is a transition from adequately circulated cells to cells that are ischemic to a degree that produces complete inactivation. Exciting factors acting upon these hyperexcitable cells in the transition zone evoke discharges. Accelerating ectopic stimuli act to decrease the refractory period and slow conduction throughout the responding myocardium, predisposing to re-entry of impulses with subsequent ventricular fibrillation.

It has been demonstrated experimentally and in terminal electrocardiograms in man that conditions which produce gradual over-all diminution in the functional capacity of the cardiac tissue, without predisposition to ectopic ventricular systoles, result in failure of the pacemaker or of A-V conduction, but very rarely induce ventricular fibrillation.[17–19] Generalized asphyxia or anoxia produces myocardial injury of the highest order, yet "injury currents" do not exist. Despite the hyperexcitability which moderate anoxia produces, it is only when a "trigger" is produced that ventricular fibrillation and sudden death occur. In the presence of generalized anoxia, perfusion of one coronary bed with oxygenated blood may be catastrophic[13] instead of beneficial.

Mechanism death is a consequence of the interaction of two factors: (1) a vulnerable area of ischemic myocardium and (2) an adequate stimulus—the "current of oxygen differential"—produced by contiguous areas of myocardium of different degrees of oxygenation.[13] This current in turn depends upon three factors: (1) the absolute difference in oxygenation of the two areas, (2) the abruptness of the transition from one area to the other, and (3) the relative area of the trigger. These factors act to produce an electrically unstable heart. It is not to be assumed that ventricular fibrillation must occur when these currents are at their maximum. The amount of current necessary is determined by the threshold of the trigger area, so that fibrillation may occur when differences of potential are decreasing. Such factors as the accumulation of abnormal or excessive metabolites, changes in potassium concentration across the contact zone, and products of tissue necrosis undoubtedly play an intermediary role.

The relation of these two factors, the current of oxygen differential and the fibrillation threshold, to the production of ventricular fibrillation may be expressed as the fibrillation index;[13] that is:

$$\textit{Fibrillation Index} = \frac{\textit{Current of Oxygen Differential}}{\textit{Fibrillation Threshold}}.$$

Thus, with a high fibrillation threshold, a large current is necessary to achieve the fibrillation index. By the same token, the fibrillation threshold may be reduced to such a low level that a negligible stimulus may be sufficient to reach the fibrillation index. Agents such as hypothermia probably predispose to ventricular fibrillation by such a mechanism.[20]

Summary and Conclusions

This presentation is concerned with 20 patients with coronary heart disease (from a series of 350 patients operated on by Dr. Claude S. Beck), in each of whom a chronic arrhythmia constituted a prominent manifestation of coronary heart disease. Long-term follow-up (one to six years after operation) reveals significant clinical improvement, associated with abolition or diminution of the arrhythmia, in 85 per cent of the series.

Within the limits of this study, these arrhythmias represent a reliable index of myocardial ischemia in a given patient with coronary heart disease. Since operation consistently exerts a favorable influence upon such arrhythmias, with concomitant clinical ("subjective") improvement, this constitutes confirmatory ("objective") evidence of the beneficial effect of operation.

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Experimental Studies

Effect of Systemic Blood Pressure and Vasopressor Drugs on Coronary Blood Flow and the Electrocardiogram*

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SUSTAINED severe shock due to acute myocardial infarction in the human is attended by a mortality rate of 80 to 90 per cent.[1,2] When vigorous measures to combat hypotension are used, however, the fatality rate is reduced from 80 to 47.8 per cent.[3] Effective control of the blood pressure has been reported with the use of noradrenalin resulting in 53 per cent clinical recovery.[4]

The basic mechanism of shock in myocardial infarction is not fully understood. It has been demonstrated[5–12] that two fundamental disturbances occur: (1) forward heart failure resulting from myocardial weakness and reduced cardiac output; (2) a peripheral vascular reaction causing (a) a failure to maintain an adequate compensatory increase in peripheral resistance in the presence of a lowered cardiac output and (b) a pooling of the venous blood. Vasopressor agents act on the peripheral vascular bed, increasing the total peripheral resistance and hence raising the systemic blood pressure. The blood flow in certain vital organs such as the kidney and intestine may be diminished when the pressor agents are used, but other vital organs such as the heart and brain will receive a supply adequate to maintain a nearly normal nutrition.[13] This project was designed to further study the hemodynamics of the coronary circulation in shock states and the effect of vasopressor drugs.

In confirmation of the apparent soundness of the vasopressor therapy of acute coronary thrombosis, it was shown by Corday and co-workers[14] that in dogs loss of contractility and ballooning of the myocardium beyond a ligated coronary artery diminishes or disappears when hypotension is corrected by blood transfusion. This was a physiologic demonstration of the effect of systemic blood pressure on myocardial function in simulated coronary occlusion.

The present study is primarily concerned with the effect of systemic blood pressure on both segments of the coronary circulation, namely, the normal forward (antegrade) flow and the collateral (retrograde) flow. It involves direct volumetric measurement of coronary flow in dogs under the effect of shock, vasopressor agents, transfusion, and aortic snare by three separate techniques: the open-drop method, the rotameter, and the photoelectric dropmeter.

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Methods and Materials

Method I. Open-Drop Method of Comparing Free Antegrade and Free Retrograde Coronary Flows: Mongrel dogs weighing 14 to 16 kg were used in the experiments. Each animal was anesthetized with intravenous Nembutal or chloralose and was well heparinized. In each case, the anterior descending coronary artery was divided and both cut ends were cannulated with maximum-sized polyethylene tubing.[15] In this manner it was possible to collect and measure the retrograde (collateral, from distal cut end) and antegrade (forward, from proximal cut end) portions of coronary flow simultaneously, but separately, in graduated test tubes for a period of one-half minute. As this blood flowed freely without passing through the peripheral coronary bed and, hence, without the influence of the peripheral coronary resistance, we called this the *free antegrade* and *free retrograde* flow.

Simultaneous antegrade and retrograde free flows were measured in 105 dogs, following fresh occlusion of the anterior descending artery by a ligature. In 5 animals, the coronary artery was ligated, the chest was closed, and recannulation of the same artery was made four weeks later to ascertain the effect of chronic occlusion on coronary flow. In 15 animals, corresponding samples were taken for oxygen studies by the Van Slyke method.

Method II. Coronary Flow Measurements with the Rotameter: The coronary flow was measured in 46 dogs by means of the Shipley rotameter.[16] The proximal antegrade and the distal retrograde coronary catheters described in Method I were connected through the rotameter so that the coronary circulation was re-established. The blood now flowed normally through the peripheral bed and the coronary resistance was thus included in the circuit.

Method III. Coronary Flow Measurements with the Dropmeter: The proximal and distal coronary catheters described in Method I were connected through the photoelectric dropmeter so that the circulation to the distal end of the cannulated coronary artery was again re-established as in Method II, thus including an intact peripheral coronary resistance. The anterior descending coronary artery flow was measured in 39 dogs. Also, simultaneous flow measurements were made of the coronary sinus, anterior descending, circumflex, and right coronary arteries in 19 other dogs. The photoelectric dropmeter was described by Marsh,[17] Lindgren,[18] and others. We modified their techniques by recording each drop individually and then converting the flow rate from drops per minute to cubic centimeters per minute using a predetermined calibration curve. This modification allowed us to visualize each drop to insure that streaming did not occur and that a uniformity of drop size persisted. The drop size varies with the rate of blood flow and this requires correction with calibration curves at higher rates of flow. The calibration curves were determined by volumetric measurement which corrected the blood flow for each individual dropper according to rate of flow and allowed us to measure the coronary flow with a greater degree of accuracy, approximating less than a 3 per cent error. Each dropper will measure up to 36 cc per minute; however, to obtain higher flow rates, the flow is divided between and recorded by 2 or 3 droppers.

Results

Observations on Antegrade and Retrograde Flow Using Open-Drop Techniques

In 48 per cent of the dogs studied, the retrograde-antegrade flow ratio determined by the open-drop method was less than 10 per cent.[15] This probably indicates that the collateral circulation was functionally relatively insignificant in these animals. In 11 per cent of the dogs, however, a ratio above 20 per cent was found. This figure probably indicates a functionally significant collateral flow.[15]

Oxygen-saturation studies were performed on the antegrade and retrograde blood. These

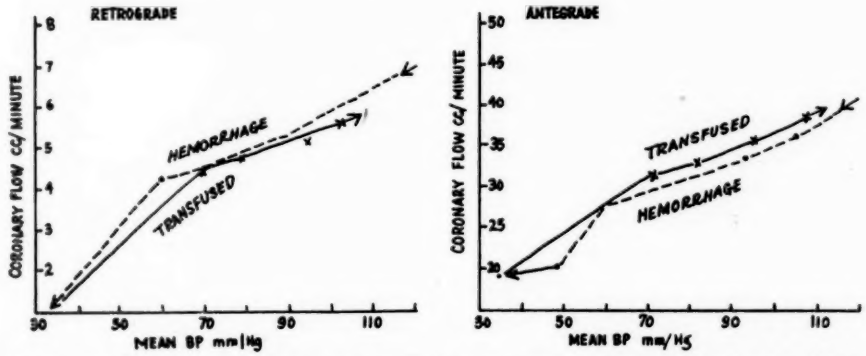

Fig. 1. Effect on the retrograde and antegrade coronary free flows of reducing the blood pressure by bleeding the animal and later raising the blood pressure by blood transfusion. Coronary flows increase with the increase in systemic blood pressure. Raising blood pressure with noradrenalin produced similar tracings.

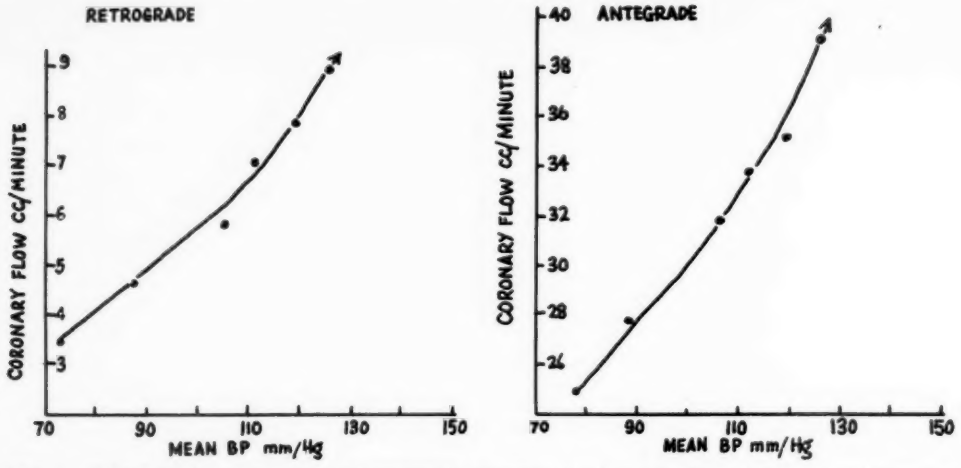

Fig. 2. Effect on the retrograde and antegrade coronary free flows of increasing the blood pressure by the administration of noradrenalin. The retrograde flow is above average because of chronic ligation of the coronary artery.

revealed that the oxygenation of the retrograde blood was equal to that of the antegrade blood, indicating that the retrograde blood was also arterial in nature.

Effect of Changes in Systemic Blood Pressure Following Acute Coronary Occlusion: In 105 dogs with fresh coronary occlusion subjected to hypotension, the coronary flow was observed to diminish markedly in a linear fashion in both the antegrade and retrograde segments. This effect is demonstrated in Figure 1 in which hemorrhagic shock was used to reduce the blood pressure. The blood pressure was later raised to various levels by either administration of blood, noradrenalin, metaraminol, or an aortic snare.

In every instance, changes in systemic blood pressure of even as little as 10 mm Hg had a definite effect on the flow. Repeatedly bringing the blood pressure down to lowest levels and back to normal or higher produced similar flow curves.

Out of the total of 105 experiments described above using the open-drop technique, only 3 showed evidence of a coronary vasodilator action of noradrenalin (Levophed) (discussed later).

Effect of Changes in Systemic Blood Pressure Following Chronic Coronary Occlusion: In the 5 dogs in this group, the results obtained were similar to those found with recent coronary occlusion. The same flow curve and the same vital

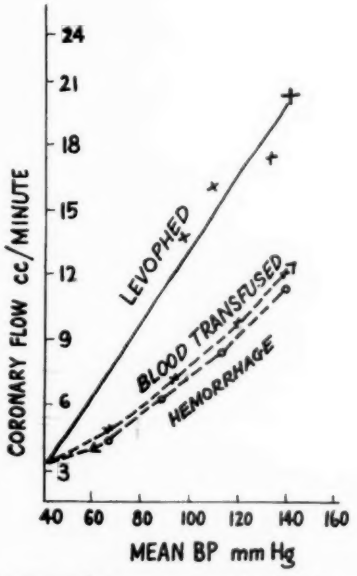

Fig. 3. Coronary flow was measured with the rotameter. The blood pressure was first reduced by bleeding the animal to 40 mm Hg. The animal was then transfused. The blood pressure was again reduced by bleeding the animal, then noradrenalin (Levophed) was administered. Note that the administration of noradrenalin caused a marked increase in the coronary flow probably due to vasodilatation of the peripheral coronary circulation or increased inotropic action.

increase in the coronary flow were noted when the systemic blood pressure was raised except the changes were of greater magnitude (Fig. 2).

OBSERVATIONS USING THE ROTAMETER

It was demonstrated that the antegrade

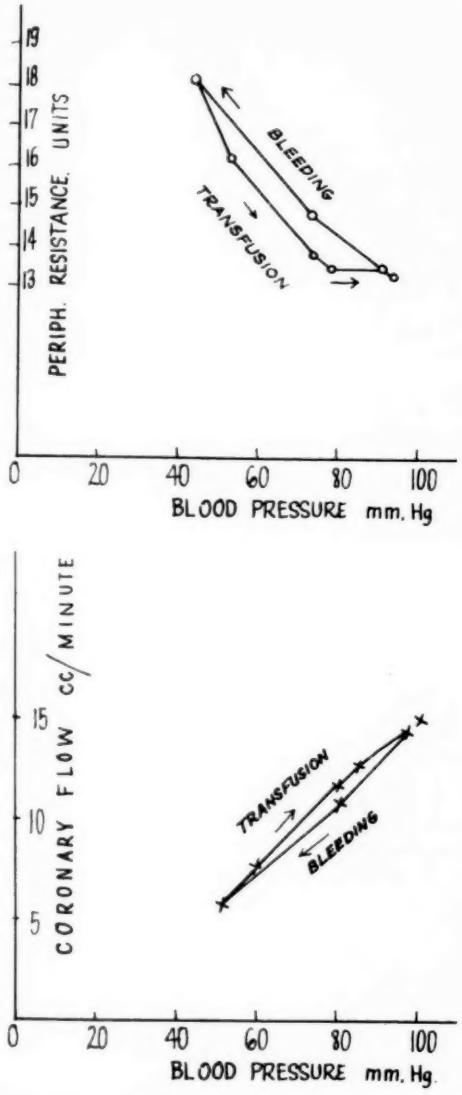

Fig. 4. Coronary flows (lower graph) and peripheral resistance (upper graph) of the anterior descending coronary artery were measured with the photoelectric dropmeter, demonstrating the effect of bleeding the animal and transfusion within a 20-minute period.

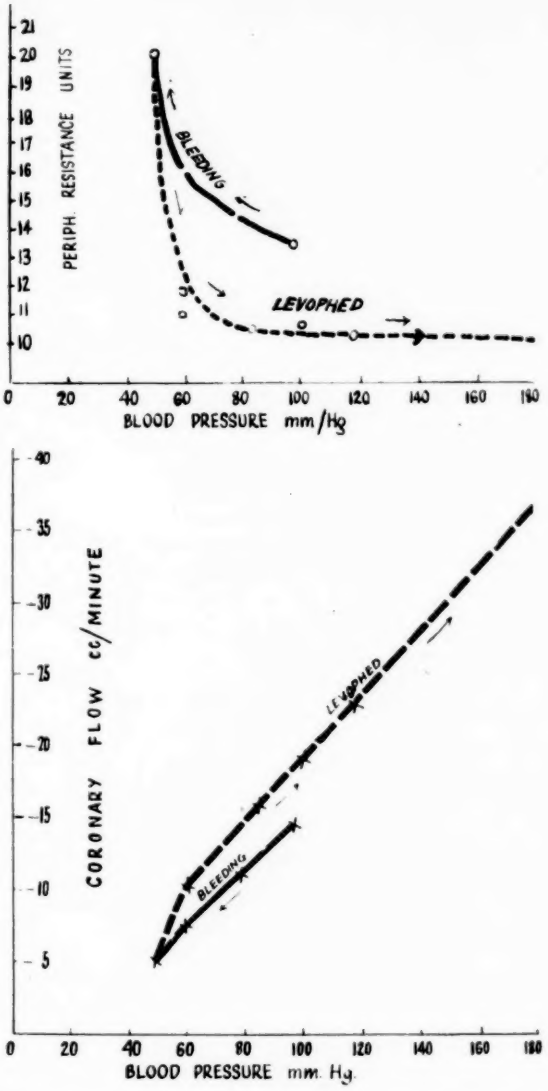

Fig. 5. Anterior descending coronary flow was measured with the photoelectric dropmeter (lower tracing). The blood pressure was first reduced to 45 mm Hg by bleeding the animal and then restored by the administration of noradrenalin. The upper tracing demonstrates the change in peripheral resistance of the coronary circulation derived from the figures of the lower tracing.

directed coronary flow increased in a linear fashion as the systemic pressure was elevated. The characteristics of the flow curve were usually linear. A coronary dilator action of noradrenalin was usually noted (Fig. 3).

OBSERVATIONS USING THE PHOTOELECTRIC DROPMETER

It was noted that as the blood pressure was lowered the coronary flow dropped in a linear fashion in the four cannulated coronary vessels (Figs. 4, 5, and 6). When the blood pressure was restored by an aortic snare or by blood transfusion, the flows increased again in a linear fashion (Fig. 4) to the levels present with the original control blood pressure. The flow characteristics of all four vessels were similar, but the change in peripheral coronary resistance

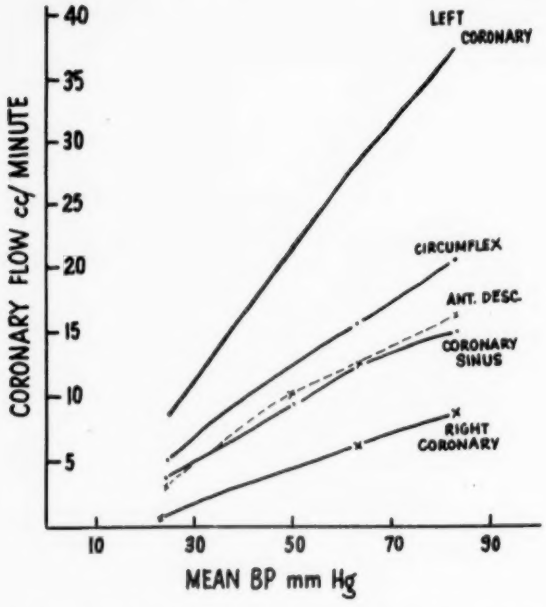

Fig. 6. Blood flow was measured with the photoelectric dropmeter of the circumflex, anterior descending, and right coronary arteries simultaneously with the coronary sinus. Following cannulation, severe hypotension resulted and the blood pressure could not be restored with blood transfusion. Note that as the blood pressure was elevated following the application of an aortic snare, the coronary flows increased in a linear fashion.

was greater in some coronary arteries than others (Fig. 6).

It is interesting to note that the ratio of the total left coronary flow to the total coronary sinus flow was not constant during cardiac arrhythmias or alterations of blood pressure. This suggests that some blood from the left coronary artery was shunted to other channels and did not return by way of the coronary sinus at all levels of pressure.[26] We doubt, therefore, that measurements of the coronary sinus flow actually reflect the true changes in the total left coronary flow at all times.

Peripheral Coronary Vascular Resistance: The peripheral coronary resistance increased as the blood pressure was lowered by hemorrhage and returned to normal or near normal when the pressure was raised with blood transfusion (see Figs. 4, 5, and 6). This confirms the recent observations of Okinaka[64] but differs with that of Osher.[19] The peripheral coronary resistance decreased considerably when the hypotension due to hemorrhage or coronary shock was corrected by noradrenalin. It fell below the control value, demonstrating that noradrenalin is a coronary dilator (Fig. 5).

Discussion

Effect of Shock on Coronary Flow

It is evident from our experimental studies that regardless of the method of measurement, the coronary artery and coronary sinus flows decrease as the blood pressure is reduced, whether by hemorrhage or surgical trauma or cardiogenic shock. As the blood pressure is again elevated, the coronary flow increases in a linear fashion in all segments of the coronary circulation. Most investigators agree with this.[19,20,51,53,63,64] However, Hackel and Goodale[21] claim that shock in the dog resulting from hemorrhage does not decrease the coronary flow despite very low systemic arterial pressure and low cardiac output. The evidence presented by these authors was obtained by the nitrous oxide coronary sinus technique. The reliability of this method for the determination of regional blood flow has been questioned by Sapirstein and Ogden.[22] Our studies using the dropmeter indicate that the coronary sinus flow does not accurately reflect the flow of the left coronary

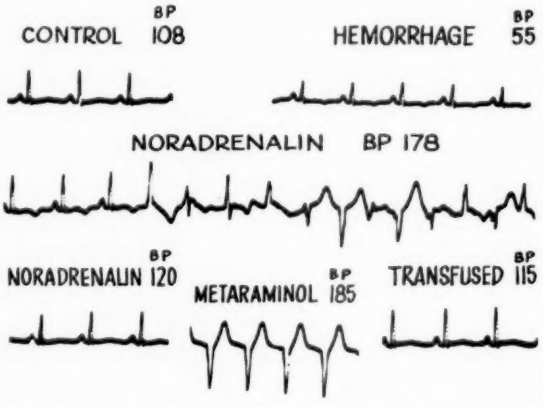

Fig. 7. Electrocardiograms (lead 2) of the dog. The chest was not opened. The blood pressure was reduced by bleeding the animal and later noradrenalin was administered. Note that the T waves became inverted when the mean blood pressure was reduced to 55 mm Hg. When the blood pressure was raised to excessive levels with noradrenalin or metaraminol, serious ventricular arrhythmias resulted. However, when the blood pressure was maintained at normal levels, the T waves again became upright.

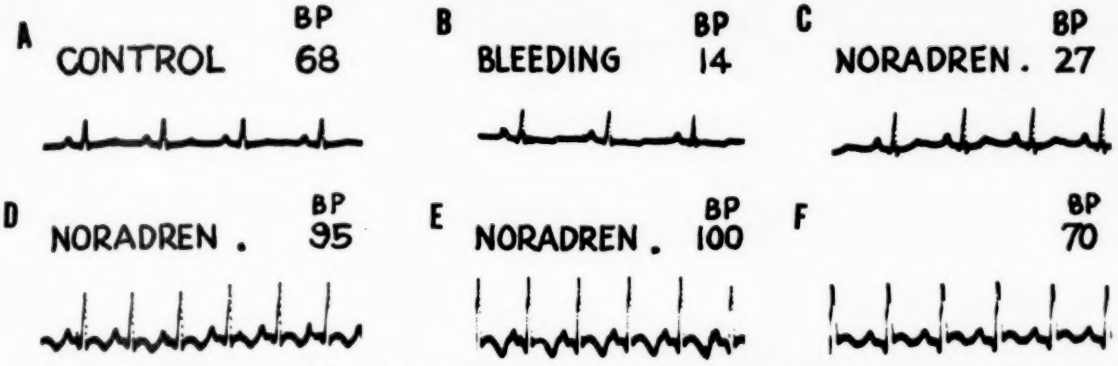

Fig. 8. Electrocardiograms (lead 2) of the dog. The chest was not opened and the heart was not exposed. The animal was bled. Note that the T waves became slightly inverted when the blood pressure dropped (*B*). When the blood pressure was raised slightly by noradrenalin, the T waves again became upright (*C*). However, when the mean blood pressure was raised above 95 mm Hg, the ST segments elevated slightly and the T waves became deeply inverted (*D*, *E*). Note that the height of the R wave became increased (*D*, *E*, *F*) after the administration of noradrenalin.

artery because of possible shunts, although it shows a similar linear relationship as the arterial flow.[26]

Shock due to acute myocardial infarction differs in many ways from that caused by hemorrhage. The results of the present study have shown a definite decrease in the coronary flow regardless of the method used to produce hypotension. Coronary flow diminishes whether hypotension is induced by bleeding, by hypotensive drugs, or following coronary artery ligation. A slight change in the systemic blood pressure of but 20 mm Hg may change the coronary flow by 30 per cent. This consideration is of the utmost importance in the clinical management of the patient.

EFFECT OF SHOCK AND VASOPRESSOR DRUGS ON THE ELECTROCARDIOGRAM

Effect of Lowered Blood Pressure: Our electrocardiographic observations were made in animals whose chests were not opened because such surgical procedures in themselves will cause electrocardiographic abnormalities. With lowering of the blood pressure by bleeding the animal, the standard limb leads of the electrocardiograms first showed a reduction in amplitude of the T wave which later became diphasic or inverted (Fig. 7). The ST segment occasionally became slightly depressed. When the blood pressure was raised by blood transfusion, the T wave became upright again (Fig. 7).

Effect of Noradrenalin: Changes in the electrocardiogram, including arrhythmias, have been observed by many during noradrenalin administration.[23–25,52,60] We observed that administration of noradrenalin initially caused the T wave to become upright, but as the pressure was further elevated toward normal, the ST segment often became elevated and the T wave became diphasic or inverted and later deeply coved (Fig. 8). After noradrenalin was discontinued and the blood pressure lowered, the T waves became less inverted and occasionally upright. The ST segment elevation was often

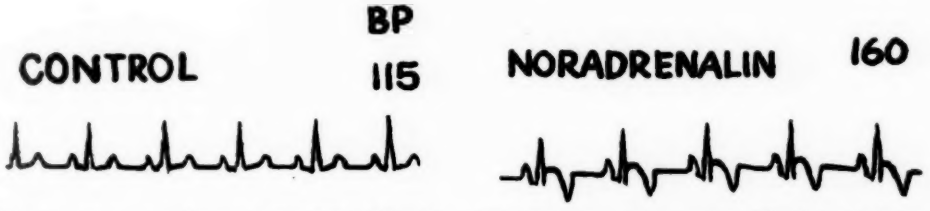

Fig. 9. Electrocardiograms (lead 2) of the dog. The chest was not opened. The heart is intact. Note that after administration of noradrenalin the ST segments became elevated and the T waves became deeply inverted and coved. This tracing would resemble that of an early myocardial infarction although the coronary arteries were completely normal.

the last abnormality to return to normal. These ST segment elevations and T wave inversions often simulated those seen in acute myocardial infarction (Figs. 8 and 9), although the coronary arteries were normal. If these changes occur in the human, they could be of great practical importance because they could be mistaken for those found in a recent myocardial infarction.

Arrhythmias Due to Excessive Hypertension: At hypertensive levels of above approximately 180 mm Hg systolic, whether due to vasopressor drug or the application of an aortic snare, arrhythmias such as nodal rhythm, idioventricular rhythm, ventricular conduction defects, multiphasic premature ventricular systoles, or ventricular tachycardia occurred (see Fig. 7). These arrhythmias terminated promptly when the drug was discontinued and the blood pressure returned to normal. The changes in rhythm, therefore, appeared to be due in part to the "excessive" hypertension. It is important that when vasopressor drugs are used, the blood pressure should be carefully monitored and kept below hypertensive levels for fear of causing fatal arrhythmias.[26] It is a paradox that vasopressor drugs will terminate auricular and ventricular tachycardias and premature systoles in the presence of hypotension, yet at excessive levels of blood pressure they may induce more serious arrhythmias.[26]

Causes of Noradrenalin-Induced ECG Changes: The explanation of these electrocardiographic changes associated with noradrenalin is not yet clear. Raab[27] states that myocardial anoxia results from excessive catecholamines because of the increased myocardial oxygen consumption caused by them. Alterations in carbohydrate metabolism which the catecholamines produce may also possibly affect the electrophysiology of the heart, producing similar ST and T wave changes.[29] Recent studies have shown that during the administration of noradrenalin a net loss of potassium from the heart occurs which results in an alteration of the transmembrane potential.[54–56,60] This shift in cellular electrolytes is thought to be a result of an alteration in the permeability of the myocardial cellular membrane produced by noradrenalin.[28] It was shown that in the presence of hypokalemia, noradrenalin caused serious arrhythmias much more readily; when the potassium concentration was raised, these serious arrhythmias were less likely to occur.[60] It may be postulated then that should serious arrhythmias develop from an inadvertent overdosage of noradrenalin, the administration of potassium intravenously should help to restore normal rhythm.

Bellet has used potassium salts successfully in certain cases of arrhythmias not associated with digitalis toxicity or hypokalemia.[65] It has been shown experimentally[66] that sodium antagonizes the effect of potassium in the heart and, therefore, it would seem that the administration of sodium salts with noradrenalin is contraindicated and may help to provoke the development of serious arrhythmias during noradrenalin administration. The presence of a high serum sodium and low potassium would seem, therefore, to be the most dangerous situation during noradrenalin administration. Further confirmatory research is required to correctly assess this problem.

EFFECT OF NORADRENALIN ON PERIPHERAL CORONARY RESISTANCE

That noradrenalin is a powerful coronary vasodilator has been demonstrated by numerous investigators.[30–33,61,62,64] Most workers agree that the coronary dilatation is secondary to the metabolic effects of noradrenalin on the myocardium. Wegria[31] concluded that the principal factor responsible for increasing the coronary flow after noradrenalin administration was the

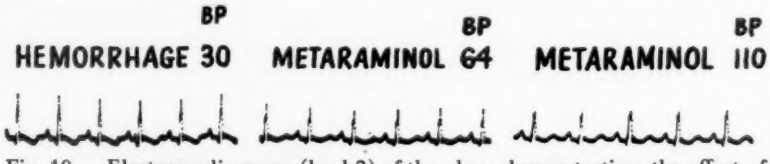

Fig. 10. Electrocardiograms (lead 2) of the dog, demonstrating the effect of elevating the blood pressure with metaraminol, following the production of hemorrhagic shock.

stimulation of myocardial metabolism resulting in the release of metabolites possessing vasodilator properties. This same view is held by the majority of workers.

However, the question of what, if any, primary action noradrenalin has on the coronary vessels is far from settled and is presently a point of controversy. The changes in peripheral coronary resistance, however, may also be due to alterations in extravascular support. Lu and Melville,[32] Berne,[59] Wiggers,[62] and Okinaka[64] believe that noradrenalin is a primary coronary vasoconstrictor. An observation by some of these workers is that a transient increase in the coronary resistance occurs immediately following the administration of noradrenalin, before the secondary coronary vasodilatation becomes manifest. From this it is concluded that initially the primary vasoconstrictive property of noradrenalin is responsible for the transient increased coronary resistance which lasts until myocardial metabolites are released which then cause a secondary vasodilatation. Denison[61] concluded from his experimental work in dogs recently that noradrenalin is a primary coronary vasodilator. Recently, Lundholm[30] demonstrated in isolated sections of bovine coronary arteries that noradrenalin exerted a direct dilatory action which occurred simultaneously with the production of lactic acid by the smooth muscle cells of the artery.

Table I compares the effect of noradrenalin and aortic snare on the coronary flow and resistance using a photoelectric dropmeter. The coronary resistance consistently shows a decrease following noradrenalin and often an increase following the application of an aortic snare. Green, Wegria, and Boyer[34] also observed an increase in coronary resistance following the application of an aortic snare. With identical increases in aortic pressure, the flows following noradrenalin administration are about twice those following the application of an aortic snare. It is obvious, therefore, that noradrenalin is a potent coronary vasodilator (see Figs. 3 and 5). In contrast, using the open-drop technique, noradrenalin did not show any vasodilator activity in either segment (free retrograde or free antegrade) (see Figs. 1 and 2).

If noradrenalin had increased the coronary flow because of a dilatation of the larger coronary arteries, then the flows using the open-drop method should have been augmented. As this did not occur, the conclusion is that noradrenalin affects only the peripheral coronary bed, reducing the peripheral resistance and increasing the coronary flow.

TABLE I

Data from Three Typical Experiments Showing Effects of Raising Blood Pressure by an Aortic Snare and Noradrenalin

	Mean B.P. (mm Hg)	Heart rate	Coronary flow (cc/min)	Coronary resistance[a]
Control	120	168	14.4	8.33
Aortic snare	165	156	16.5	10.00
Noradrenalin	168	150	25.0	6.72
Control	75	168	7.6	9.86
Aortic snare	120	120	8.0	15 00
Noradrenalin	122	120	19.2	6 36
Control	70	126	8.0	8.75
Aortic snare	140	96	10.2	13.72
Noradrenalin	139	98	16.2	8.60

[a] Mean B.P./coronary flow.

THE COLLATERAL CORONARY CIRCULATION

As stated before, the open-drop technique reveals that noradrenalin increases the retrograde free flow in the distal cut end of a coronary artery as the blood pressure is elevated but does not cause vasodilatation. By rotameter and dropmeter methods, we have demonstrated a decrease in the resistance of the peripheral coronary bed with noradrenalin, and this suggests that the free retrograde coronary flow is derived from intercoronary anastomosis and that the flow does not pass through the peripheral bed. This is confirmed by the fact that the retrograde free flow is arterial in nature. If it had passed through the peripheral bed, the oxygen saturation would have been reduced. These studies indicate, therefore, that the collateral circulation is mainly arterial in nature and is not influenced by noradrenalin except by the mechanical effect of an increase in the aortic perfusion pressure.

The need for a good collateral circulation in

coronary thrombosis cannot be overemphasized. Certainly, the viability and function of the myocardium beyond the site of occlusion depends upon effective nutrient collaterals. To this effect, Wiggers[62a] has aptly remarked, "The rapid necrosis of cardiac tissue could scarcely occur, were adequate anastomoses present."

The importance of the collateral coronary circulation, of course, is predicated on its inherent normal function and on its potential development. Were the coronary vessels absolutely dead ends and the intercoronary connections utterly functionless, remaining incapable of further growth or improvement, the hope for amelioration of coronary artery disease would have long been a closed chapter.

Augmentation of Collateral Circulation: Fortunately, as various authors[35–41] have shown, the collateral coronary circulation is not devoid of some degree of functional significance. Following experimental or clinical acute occlusion of a coronary artery, the area of infarction is smaller than the entire territory of distribution of that artery and its branches. Blumgart *et al.*[42] and Schlesinger[43] have observed that 15 per cent of normal human hearts reveal large interarterial communications and that 98 per cent of hearts with occluded arteries have "collateral channels which are more numerous, occasionally visible to the naked eye, and of great functional significance."[43] We have demonstrated that in only 11 per cent of beating dogs' hearts, the collateral circulation is above 20 per cent of the antegrade flow.[15] Improved collateral circulation by prolonged occlusion of a major coronary artery has been observed in dogs by Gregg *et al.*[44] and in pigs by Blumgart *et al.*[42] We have confirmed their findings in the beating dog's heart.

Despite all these classical observations on the physiologic significance of the normal interarterial connections and on the circumstances which may lead to their augmentation or improvement of function, no description has been made of a method whereby one can suddenly improve the collateral coronary circulation in an acute episode of coronary thrombosis. Coronary vasodilators such as xanthines and nitrates may augment collateral flow, as demonstrated by Gregg.[16] However, they would be worthless in the face of critical hypotension, because they depress the systemic blood pressure to lower levels. Our experimental studies show that a simple elevation of the systemic blood pressure effectively increases the collateral circulation.

IMPROVEMENT OF CORONARY FLOW BY ELEVATION OF SYSTEMIC BLOOD PRESSURE

In view of the obvious deleterious effect of shock or hypotension on the coronary circulation, it would seem necessary to maintain an adequate systemic blood pressure at all times. Extreme hypotension, as in late hemorrhage, can cause ventricular failure,[45] coronary insufficiency, or even myocardial infarction in the absence of coronary artery narrowing.[46] It appears that such complications can be prevented if the hypotension is corrected promptly. Similarly, it would appear that even less marked hypotension can cause severe damage to the heart in the presence of coronary narrowing or occlusion. A drastic reduction in the coronary flow may precipitate cardiac arrhythmias, which frequently disappear upon improvement of the blood pressure.[26] Antihypertensive drug therapy is capable of aggravating angina pectoris in hypertensive patients with coronary artery disease.[47] It logically follows that care should be taken not to reduce the blood pressure excessively in order to avoid provoking more severe angina.

Control of Blood Pressure in Coronary Thrombosis: In coronary thrombosis, it is necessary to muster all available coronary function and maintain it at the best possible level. Maintenance of coronary flow to provide nourishment of the myocardium and thus prevent heart failure and arrhythmias appears feasible with proper elevation and control of the systemic blood pressure. An arbitrary level from which to start raising the blood pressure may not be necessary in this connection. Clinical judgment will, of course, be the best guide, but the previous level of blood pressure must be taken into consideration. When the patient develops congestive failure or arrhythmias at low normotensive levels, it may be wise to elevate the blood pressure to a slightly higher level since

we have shown that raising the blood pressure 20 mm Hg may augment both the forward or collateral coronary flows by 30 per cent. We have demonstrated that premature systoles, supraventricular and ventricular tachycardia and bradycardia can often be corrected with restoration of blood pressure.[26] Malach[48] recently demonstrated a much lower mortality rate in patients who remained hypertensive following a coronary occlusion compared to a normotensive control group. Successful clinical results in the treatment of acute myocardial infarction with shock seem to correspond with the use of vasopressors, such as noradrenalin.[1–4,14,49] This observation runs parallel with ours in the present studies. We have noted that serious arrhythmias can be provoked if the blood pressure is raised to markedly hypertensive levels (above 180 mm systolic) but can be terminated when the blood pressure returns to normotensive levels. Therefore, an easily controlled, short-acting vasopressor drug such as noradrenalin should be used to prevent these serious arrhythmias and the attending staff should be familiar with dangers of excessive hypertension.

The importance of even a few additional drops of blood to an infarcted area cannot be overestimated. From experimental evidence, Beck concluded that "drops of blood added to or taken away from an area of muscle already made ischemic by arterial occlusion makes the difference between life and death." In the present study, it has been demonstrated that the collateral flow of the occluded anterior descending artery can be augmented by as much as 4 cc per minute (60 per cent) by merely raising the systemic blood pressure 30 mm Hg. If a significant collateral circulation is not yet established, as in a young individual, the vasopressor drugs will be less effective in nourishing an ischemic area of myocardium.

Summary and Conclusions

The effect on coronary flow of variations of systemic blood pressure was studied in dogs with fresh coronary occlusion and with chronic coronary occlusion. Hypotension was always accompanied by a significant decrease in coronary flow in both the antegrade and collateral coronary circulations. Elevation of the blood pressure was accompanied by a significant increase in coronary flow for both segments of the coronary circulation. Raising the blood pressure just 20 mm Hg often elevated the coronary flow 30 per cent.

The clinical significance of reduction of coronary flow by shock or hypotension has been reemphasized. The importance of restoring and maintaining the blood pressure in coronary artery disease has been stressed, especially where the coronary flow needs prompt and effective improvement, as in shock due to acute myocardial infarction. Prompt use of vasopressor drugs may prevent or limit necrosis of an ischemic myocardium following a coronary occlusion. The clinician should not be guided only by the absolute level of systemic blood pressure before instituting vasopressor therapy but by the relative changes of pressure with the clinical conditions of the patient. The presence of heart failure or cardiac arrhythmias following coronary occlusion warrants institution of vasopressor therapy even with a small drop in blood pressure. A slight rise in systemic blood pressure can cause a profound increase in coronary flow.

Electrocardiographic abnormalities caused by hypotension and vasopressor drugs are described, some of which might erroneously be considered due to a recent myocardial infarction.

Acknowledgment

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Effect of Glyceryl Trinitrate (Nitroglycerin) on Arterial Blood Supply to Ischemic Myocardium*

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The literature on the action of the vasodilating drugs is voluminous; the methods of study used were many and varied; and the interpretation of these results was found often to be contradictory. Therefore, while a survey of the literature seemed a necessary preliminary to the writing of this report, no useful purpose would be served by detailing the survey or enumerating again the methods of investigation that were used.

Even after studying the literature, we are not able to make a simple statement concerning the effect of nitroglycerin. For a drug used so much this is difficult to believe. Excerpts from several articles together with our comment may be in order.

Historical Background of Vasodilating Drugs

Wiggers and Green[1] published an article entitled "The Ineffectiveness of Drugs upon Collateral Flow After Experimental Coronary Occlusion in Dogs." This title in itself leaves no doubt that authority has spoken. The following quotations are taken from this article:

> Opinion is still at variance as to the completeness of the ischemia which follows total occlusion of a large coronary branch and as to the chances of promptly starting sufficient collateral blood flow by use of drugs to prevent *contractile failure* or to minimize the succeeding *necrosis* and *fibrosis*. . . . A sufficient sampling of possible useful drugs by these methods necessitates, we regret, the conclusion that an increase in collateral circulation sufficient to be of functional use cannot be obtained by the use of vasodilating drugs after complete coronary occlusion.

The scientist appreciates this emotion of regret and recognizes that these physiologists were concerned only with contractility and viability of muscle. At the same time the patient with the disease suffers from anginal pain and lives in fear of sudden death, and neither pain nor sudden death is related to viability and contractility of muscle (Fig. 1).

Gregg,[2] after spending a lifetime in the study of the physiology of coronary heart disease, stated:

> Through lack of adequate methods, great confusion still exists as to the mechanism of drug action, and in most instances, no definite statement can be made.

In 1951 Wegria[3] published an article on the pharmacology of the coronary circulation with 190 references. He stated:

> The reviewer hopes to have pointed out that to gain complete knowledge of the effect of a drug on the coronary circulation it is mandatory to investigate the effect of that drug not only on simple, very artificial preparations but also on more complicated preparations including ultimately unanesthetized healthy and sick human beings. It hardly needs to be said that a great deal remains to be done.

This author does not define the problems of coronary heart disease in order to give proper direction to the research for the future and simply calls for more work. It is obvious that the disease is poorly understood and we scarcely know what to study and measure.

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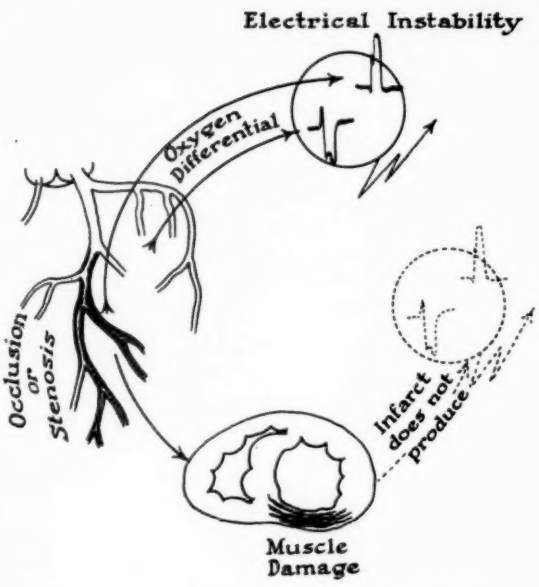

Fig. 1. Sequelae of stenosis or occlusion, two independent biological responses: (1) muscle damage; (2) oxygen differentials, anginal pain, electrical instability, ventricular fibrillation. Viability of muscle has no relationship to the electrical condition which can kill without an infarct. To consider muscle damage only is to miss the most important aspect of the disease. (Figures 1 and 2 from Beck, C. S.: *J. Thoracic Surg.* 36: 329, 1958; reproduced by permission of the C. V. Mosby Company.)

On the clinical side, Winsor and Scott[4] found that nitroglycerin relieved anginal pain more effectively than did a placebo, whereas Master, Jaffe, and Dack[5] reported opposite results. Russek, Zohman, and Dorset[6] made a study on the effect of nitroglycerin on the electrocardiogram. Sixty patients were selected, each of whom showed positive electrocardiographic alterations produced by exercise. When nitroglycerin was given five minutes before exercise the electrocardiogram remained normal in 45 patients, and in the remaining 15 patients the abnormalities were reduced. Sixteen drugs were investigated in this way, and nitroglycerin, papaverine, and pentaerythritol tetranitrate were considered to be worthy of continued clinical use.

Even the clinicians disagree on the use of drugs. However, the patient knows whether or not a drug helps him, and the experiences of the patient should take precedence over anything else. We seem to have learned, with our many methods of study, so much that is not so.

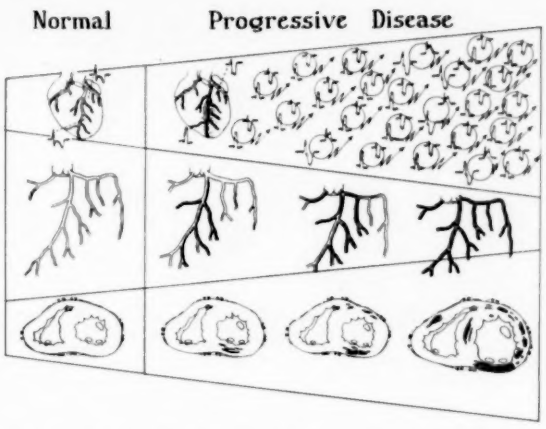

Fig. 2. Three death factors in coronary heart disease. *Top*, an unstable electrical condition; *center*, reduction of arterial inflow to terminal stage; *bottom*, destruction of muscle to terminal stage. These factors may occur separately or in any combination. Usually one is dominant and the others are secondary. The electrical factor is a constant threat. If it can be removed from consideration then the other two factors can more readily be understood. Inflow reduction without the electrical factor can proceed to almost total occlusion of all arteries before it kills and this reduction can occur without infarct. Muscle destruction without the electrical factor can kill when total inflow is not enough to support the heart beat. This analysis gives definition to the factors of this complex disease which should be measured.

The Factors That Kill

Coronary heart disease kills in three ways:[7] (1) by self-electrocuting currents produced in the heart itself from differences in oxygen content in areas of muscle that are in juxtaposition; (2) by reduced arterial inflow which has become inadequate to support the heart beat; (3) by destruction of muscle so that there is not enough contractile power to circulate the blood. These are illustrated in Figure 2.

Electrical Instability: The fibrillating currents kill the vast majority of the victims. Total coronary inflow in most instances is adequate or more than adequate to support the heart beat, but the distribution of blood is uneven (checkerboard) and an unstable electrical condition is produced. The coroner performs a necropsy on these victims of the disease and often has difficulty in explaining the cause of death because the cause is electrical and not anatomic. Structurally the heart is often too good to die.

We refer to these differences in oxygen content as "oxygen differentials."[8] These dif-

ferentials also produce anginal pain. Cyanosis throughout the entire heart is not painful. A "blue baby" does not have anginal pain, but the child with one coronary artery arising from the aorta and the other from the pulmonary artery cries out in pain and dies an electrical death. A laboratory experiment also demonstrates this physiology. A dog is anesthetized; the intratracheal tube is clamped off for 6 to 9 minutes; the entire dog becomes cyanosed and so does the heart. The heart remains electrically stable; it does not fibrillate; it stops in standstill. If well-oxygenated blood is perfused into a coronary artery of this heart it readily fibrillates. Thus, well-oxygenated (arterial) blood can kill the heart beat.

The heart also electrocutes itself when a coronary artery is stenosed or tied off in a uniformly pink heart; self-electrocution happens in tens of thousands of humans each year in this country. These deaths occur while the victim is on the golf course, shoveling snow, watching athletic contests, at the office, during physical exertion, and even at rest in bed.

Reduction of Coronary Inflow: The second cause of death is due to reduction in inflow. To exclude the electrical deaths as the stenosing disease progresses and inflow is reduced, it is necessary for the stenosis to progress with some degree of uniformity in the various arteries. Stenosis can then proceed to the point of inflow inadequacy and can occur without a gross infarct. The normal coronary arteries carry much more blood than the heart can use, and it is interesting that in the presence of an even distribution by intercoronaries the inflow can be completely closed off except for a lumen of 1 mm in one artery for the dog and 1.5 mm for the human. An even distribution of this blood is necessary so that red blood cells, after getting through the stenotic segment, can go anywhere within the substance of the heart where it can do the most good.

Destruction of Heart Muscle: The third cause of death is destruction of muscle. One artery after another becomes occluded; one segment of muscle after another is destroyed. The electrical condition is not sufficiently disturbed to cause fibrillation of the heart. Finally, the heart fails and death, when it occurs, is neither sudden nor unexpected. The patient with severe muscle destruction has been treated for heart failure. Total inflow, if evenly distributed before failure appeared, might have been adequate to support the heart beat and, if evenly distributed, might have helped to preserve contractility and viability of muscle. Thus an even distribution can delay the advent of inflow inadequacy and muscle failure. Intercoronaries are a protective factor in each of the three types of the disease. The earlier they are produced in the course of the disease the more protective do they become.

Combination of Factors: Various combinations of these disease factors may occur in the same heart. Thus a heart can electrocute itself in the presence or absence of a scar. Fibrillation may occur when a patient is in failure. Inflow reduction can stop the heart in asystole, but any small external stimulus can cause it to fibrillate. Inflow reduction and death may occur in the presence or absence of a scar.

What To Measure

This analysis of the death factors opens the disease to scientific scrutiny. These factors are so different as to represent three different diseases. This classification puts some light on the subject and gives some direction to the research.

It is obvious that the vasodilating drugs should be studied in relation to the first factor, anginal pain and electrical death. Pain and the fear of sudden death concern the patient. We can assume that the drugs cannot retard, prevent, or resolve disease in the arteries. We can assume also that they cannot resolve scar formation. If they can add some blood to ischemic muscle, then they can stabilize the electrical condition and reduce pain and the likelihood of fibrillation. If the drugs can add blood to ischemic muscle they can reduce the size of the scar when an artery becomes completely blocked off, but this additional blood must be available at the crisis when occlusion occurs. We also know that no drug makes intercoronary channels and their action is temporary. All drugs have these limitations. In expecting too much from them it is possible to miss what they can accomplish.

The essential problems in the study of vasodi-

lating drugs are (1) to produce a segment of ischemic muscle as related to contiguous muscle; (2) to measure the amount of blood in this ischemic muscle before drug action; (3) to measure augmentation of this blood after the use of these drugs. Any addition of blood reduces the oxygen differential and the electrical instability. It is obvious that the key to drug action must be based upon a determination of oxygen differentials (or blood supply) with and without the drug. This is direct measurement. All other methods involving forward flow, pressures, resistances, venous outflow, etc., are of secondary importance.

How Much Blood Is Significant for Ischemic Muscle?

The relationship between total coronary artery inflow and distribution of the blood that is in them was presented by the senior author in 1935.[9,10] It was pointed out that a small area of ischemic muscle killed the heart beat when total inflow was normal. The importance of small amounts of blood in the range of drops or a few cubic centimeters per minute made available to this ischemic area was discussed. The term "trigger mechanism" was applied to this in 1941,[11] and the concept of oxygen differentials was presented in 1955.[12] On the basis of experiments carried out by Leighninger,[13,14] 5 cc per minute in ischemic muscle (as measured by backflow determinations) saved the life of the dog when the descending ramus of the left coronary artery was ligated, and 6.5 cc did the same thing when the circumflex ramus was ligated. This was not without the development of an infarct. A few additional cubic centimeters per minute available to ischemic muscle prevented infarction.

The value of drops or cubic centimeters of blood per minute added to or taken away from ischemic muscle deserves true recognition. Without this knowledge the physiologic studies of the disease have no meaning. It seems difficult or almost impossible to learn this fact. What we need is not more work but better understanding.

Axiom for Protection

When a coronary artery becomes occluded the fate of the patient depends upon the amount of blood available to the ischemic muscle. If a certain amount of blood is available, the patient lives; if less than this amount is available, the patient dies. Anything that increases the amount is beneficial; anything that reduces it has the opposite effect. This axiom or self-evident truth is the elementary starting point as related to effective therapy.

MEASUREMENT

The amount of blood available can be measured by backflow determinations. This method was described by Anrep and Hausler[15] in 1928 and by Mautz and Gregg[16] in 1937. It has been extensively used in our laboratory and we have had a large experience with it. It satisfies the requirement for direct measurement of the blood available to ischemic muscle and we attach great importance to this method.

When the circumflex ramus or the descending ramus of the left coronary artery is ligated the requirement of localized ischemia is met. Localized ischemia, with its oxygen differential, is distinct from other conditions of oxygenation in which there is cyanosis but no differential. By cutting the artery distal to the ligature and by measuring the amount of blood that escapes from this cut artery, we get a measurement of the amount of blood that is in the arterial bed of this ischemic muscle.

According to Anrep and Hausler, it is possible for some of the blood in the arterial bed to be forced through the capillary bed by the contractile force of the muscle, but the anoxic muscle has little or no contractile power. If any blood goes through the capillary bed it is lost to measurement, since it cannot be recovered from veins because of their many anastomoses one with another. The backflow measurement, with or without a possible small loss, is a measurement of blood available to ischemic muscle.

The third requirement of method is the introduction of the factor which is to be measured. Thus the difference in backflow before and after the use of nitroglycerin is a measure of the effect of this drug. There are several variable factors in these measurements. One

concerns aortic pressure which should be kept at a constant level. Another concerns the degree of anoxia which, if increased by allowing the backflow to escape, will augment quantity. For this reason the backflow is determined for short periods, i.e. for 30 seconds.

Experimental Studies

Normal, healthy mongrel dogs, with an average weight of 40 pounds, were anesthetized with intravenous pentobarbital sodium. The jugular vein was cannulated for perfusion of blood or drug, or for bleeding the animal (Fig. 3, *A*). The chest was opened in the left fifth interspace, and the origin of the circumflex artery dissected free for a distance of about 3 mm. The dog was given 15 to 20 cc heparin intravenously. The aorta was cannulated by way of the carotid artery (Fig. 3, *B*). The circumflex artery was completely ligated near its origin and the distal segment cannulated (Fig. 3, *C*). The inside diameter of the cannula measured 1.5 mm. Arterial blood was brought from the aorta, by way of the carotid cannula and tubing, to the circumflex artery cannula to perfuse the circumflex area of myocardium. The aortic blood pressure was measured with an aneroid manometer connected to the carotid cannula (Fig. 3, *D*). A second connection (Fig. 3, *E*) in the perfusion system was made to an electromanometer to calibrate the aneroid manometer, to measure and record aortic pressure and, when perfusion of the circumflex artery was stopped (Fig. 3, *F*), the peripheral coronary artery pressure. A side tube (Fig. 3, *G*) connected near the circumflex artery cannula was adjusted so that the end of the tube was at the same level as the heart. During a backflow determination, the mean aortic pressure was kept at 100 mm Hg (±3 mm). The dog was bled or the descending thoracic aorta compressed, if necessary, to maintain a constant mean aortic pressure.

A backflow measurement was obtained by stopping perfusion of the circumflex artery with a clamp (Fig. 3, *F*) on the tube from the carotid cannula, opening the

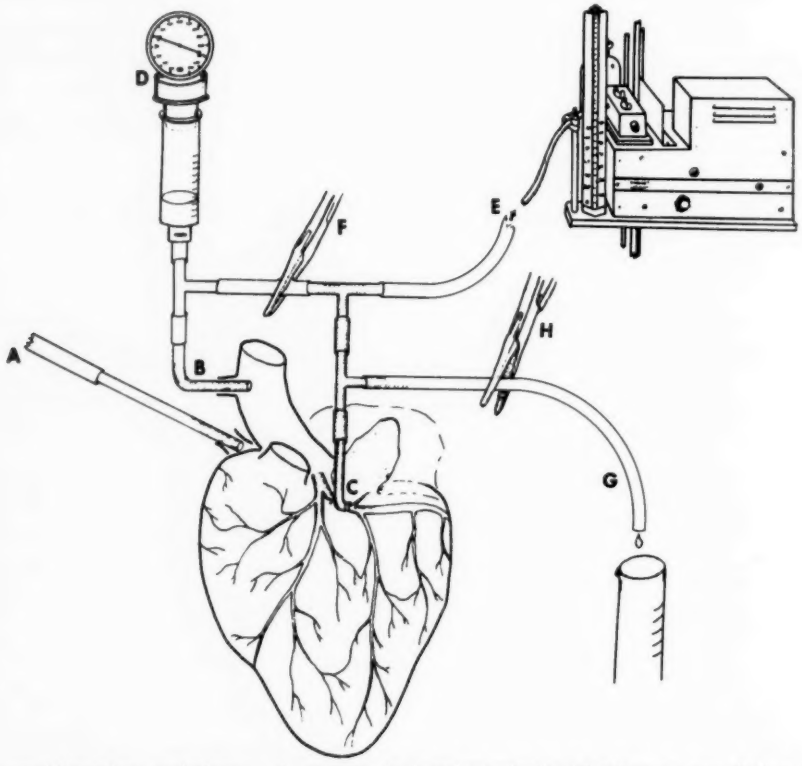

Fig. 3. Experimental backflow technique. *A*, cannula in jugular vein for bleeding or transfusing animal to adjust blood pressure and for administration of drugs. *B*, cannula in carotid artery. *C*, cannula in distal segment of ligated circumflex artery. *D*, aneroid manometer for continuous observation of aortic blood pressure. *E*, side tube to electromanometer. With this instrument the aneroid manometer is calibrated, the mean aortic pressure is recorded when clamp *F* is open and clamp *H* is closed, or the peripheral coronary artery pressure is recorded if both clamps *F* and *H* are closed. *F*, clamp on tube carrying arterial blood from aorta to circumflex artery. This clamp is open during the perfusion interval and clamped during a backflow determination. *G*, side tube with open end at level of heart. During a backflow determination arterial blood flows from unoccluded coronary arteries, across intercoronary communications, out cannula *C* and tube *G* and is collected for a period of 30 seconds. *H*, clamp on tube *G*. During backflow determination this clamp is open and during the perfusion interval it is closed.

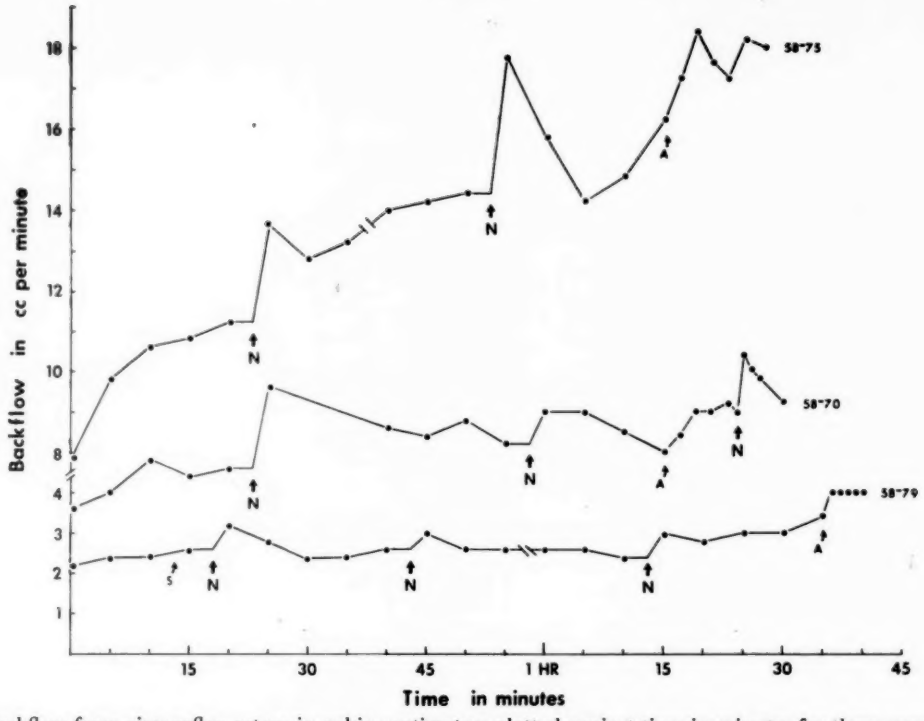

Fig. 4. Backflow from circumflex artery in cubic centimeters plotted against time in minutes for three representative dog experiments. Dog number at the right of each curve. Each dot represents a backflow measurement. At point *S* a sham injection using 1 cc saline was given. At point *N* nitroglycerin was given. At point *A* determinations were made at rapid intervals to produce maximum anoxia effect.

clamp (Fig. 3, *H*) on the side tube from the circumflex cannula, waiting 2 seconds to obtain a uniform flow, and collecting the backflow blood in a graduated cylinder for 30 seconds. Bleeding to atmospheric pressure was then stopped by clamping the side tube, and perfusion of the circumflex area resumed by opening the aortic cannula. The amount of backflow blood obtained in 30 seconds was measured and expressed in terms of cubic centimeters per minute.

Backflow determinations were repeated at 5-minute intervals until at least three consecutive determinations did not vary by more than an average of 0.2 cc per minute. Nitroglycerin, 0.6 mg dissolved in 1 cc physiologic saline solution, was then injected into the jugular vein 3 minutes after a backflow determination and 2 minutes prior to the next determination. The injection was followed by a transient drop in systemic blood pressure of about 40 mm Hg. The pressure usually returned to 100 mm by the time (2 minutes) the backflow measurement was made. In the few cases in which the pressure had not returned, it was brought back to 100 mm Hg by partial compression of the descending thoracic aorta.

In 9 instances, the dog was given a "sham" injection of 1 cc physiologic saline solution as a further control. If more than one drug injection was made on a dog, sufficient time was permitted for the drug effect to wear off and the backflow to stabilize again before another injection of nitroglycerin was given. The effect of nitroglycerin was observed 43 times on 21 normal dogs and 10 times on 6 dogs that had previously had one of several heart operations.

In 10 instances, backflow determinations on 9 dogs were made at 1-minute or 2-minute intervals, to obtain the maximum anoxia effect. Nitroglycerin was then given to determine whether there was an additional effect from the drug.

Results

Types of Response to Nitroglycerin: Three general patterns of response to the experimental conditions were observed. Examples are illustrated in Figure 4, in which the entire series of backflow determinations for each of three representative dogs are plotted against time. The time of nitroglycerin injection or sham injection, and rapid determinations to obtain anoxia effect are shown. The backflow values for dog 58-79 (Table I, experiment 16) tended to remain constant for the duration of the experiment. There was an average response to nitroglycerin, and the backflow returned to the control level within 5 to 10 minutes after each injection.

Dog 58-70 (Table I, experiment 8) showed the most common type of response. There was an early, moderate rise of backflow values to a plateau. After each response to nitroglycerin, the backflow fell to a new, higher plateau within 5 to 10 minutes.

The third pattern of response is illustrated by dog 58-75 (Table I, experiment 12). There was a slow, steady climb of backflow values to a high plateau. The response to nitroglycerin in these dogs usually was greater than in other dogs. A new, higher plateau was established after the nitroglycerin response.

Effect of Nitroglycerin on Coronary Backflow: The effect of nitroglycerin in 43 determinations on 21 normal dogs is shown in Table I. The experiment number is shown in the first column, the backflow obtained 3 minutes prior to the injection of nitroglycerin is shown in the second column, the backflow obtained 2 minutes after the injection of nitroglycerin is shown in the third column, and the increase resulting from the nitroglycerin is shown in the fourth column. Additional backflow values in these experiments are not shown. Backflow values for the other experiments mentioned above also are not shown. The results of statistical calculation of these values, however, are shown below.

The average control backflow is 4.4 cc per minute. The average increase following intravenous injection of nitroglycerin (0.6 mg) is 0.88 cc per minute. Statistical calculation of these differences reveals a standard deviation of 0.922, a standard error of 0.1406, a t of 6.2581, and a probability less than one chance in 500,000,000. This is a highly significant difference.

The average difference between two backflows immediately prior to nitroglycerin injection is 0.02 cc per minute. The standard deviation is 0.254, standard error is 0.039, and t is 0.0513 ($p > 1.0$), which supports the "null hypothesis" used in the calculation of t for the difference in backflow following injection of nitroglycerin.

The average increase in backflow following the injection of nitroglycerin superimposed on the anoxia effect is 0.2 cc per minute, which is not a statistically significant difference ($p > 0.5$).

TABLE I

Coronary Artery Backflow (cc per min) in Normal Dogs Before and After Nitroglycerin

Experiment	Before (3 min)	After (2 min)	Increase
1	1.6	2.0	0.4
2	2.0	2.8	0.8
3	3.0	4.2	1.2
4	8.0	8.8	0.8
	11.2	11.4	0.2
5	5.0	5.8	0.8
	4.8	6.2	1.4
6	1.2	1.4	0.2
	1.4	1.6	0.2
7	3.0	4.8	1.8
	3.2	4.0	0.8
8	4.6	6.6	2.0
	5.2	6.0	0.8
9	11.8	13.6	1.8
10	2.0	2.6	0.6
	2.0	2.2	0.2
	2.2	2.4	0.2
11	3.4	3.8	0.4
	4.2	4.6	0.4
12	11.2	13.6	2.4
	14.4	17.8	3.4
13	5.0	9.0	4.0
14	2.0	2.2	0.2
	2.2	2.8	0.6
15	7.0	8.8	1.8
	7.2	10.2	3.0
16	2.6	3.2	0.6
	2.6	3.0	0.4
	2.4	3.0	0.6
17	2.0	2.4	0.4
	2.0	2.4	0.4
	2.6	3.0	0.4
18	3.0	3.0	0.0
	2.8	3.2	0.4
	4.0	4.4	0.4
19	5.0	6.4	1.4
20	7.4	7.8	0.4
	7.8	8.0	0.2
	6.8	7.6	0.8
21	2.6	3.4	0.8
	4.0	4.2	0.2
	3.2	3.4	0.2
	3.4	3.6	0.2
AVERAGE	4.49	5.37	0.88

The average difference for 9 "sham" injections is −0.06 cc per minute, which is not a significant difference ($p > 1.0$).

The average difference in backflow after

nitroglycerin in 10 determinations on 6 previously operated dogs is 1.34 cc per minute. This is a significant difference ($p < 0.02$). The average control backflow in these dogs is 4.7 cc per minute.

In order to determine if the degree of response to nitroglycerin is related to the magnitude of the control backflow value, the total group of 53 control values in 27 dogs was arbitrarily divided between those values greater and less than 7.0 cc per minute. There were then 10 determinations on 6 dogs having an average control backflow of 9.4 cc per minute and 42 determinations on 22 dogs having an average control backflow of 3.08 cc per minute. The difference between these average control backflow values is 6.32 cc per minute.

The average difference in backflow after nitroglycerin was 1.94 cc per minute in the high-backflow dogs (20 per cent of the control backflow). The average difference after nitroglycerin in the low-backflow dogs was 0.74 cc per minute (24 per cent of the control backflow). These differences were compared by statistical methods, and t is 2.364 and $p < 0.05$, which is a statistically significant difference.

The increased backflow resulting from nitroglycerin injection usually lasted no longer than 5 to 8 minutes. An effect attributable directly to the drug could not be demonstrated 10 to 15 minutes after the injection.

Discussion

Backflow blood comes into the circumflex artery by way of intercoronary arterial communications from the unoccluded coronary arteries. The number of normally existing intercoronary communications varies in the dog. After a coronary artery is occluded, the amount of blood reaching ischemic myocardium depends upon the number and size of intercoronary communications bridging the artery distal to the occlusion with unoccluded arteries. The amount of blood carried by existing intercoronaries primarily depends upon the pressure differential between the aorta and atmospheric pressure when the artery is bleeding into air, and between aorta and the peripheral coronary pressure when the artery is occluded and not bleeding into air. The amount of backflow blood also depends upon coronary flow as affected by the coronary arteriolar resistance.[17] It is thought that coronary vasodilating drugs most likely act by their effect on the arteriolar resistance.[18] Coronary flow is also affected by anoxia. In order to minimize the influence of factors other than drug action, the mean aortic pressure was maintained at 100 mm Hg and backflow determinations were made at 5-minute intervals. The effect of anoxia sustained during a 30-second backflow determination would have subsided 1 to 3 minutes after reperfusing the artery.[2]

It is postulated that in the normal dog heart there may be a few intercoronary channels which do not function except after certain stimuli have opened them. The response seen in dog 58-79 (Fig. 4) would indicate that a few intercoronaries were present but that potential channels did not exist.

The most common response, illustrated by dog 58-70, was a moderate climb in backflow values to a plateau. This increase could be explained by the opening of potential intercoronary channels in response to experimental conditions. Following the stimulus of nitroglycerin, a few more potential channels opened and remained functional, as shown by the higher plateau obtained after the drug effect had subsided. The response seen in dog 58-75 illustrates a more extensive opening of potential channels.

The existence of potential channels would help explain some of the immediate benefit frequently observed in patients following a Beck operation.

The Nitroglycerin Unit

Nitroglycerin augments the amount of blood available to ischemic muscle by 0.88 cc per minute. This drug effect lasts 5 to 10 minutes. These facts were determined by direct measurement. Scientific interpretation of this amount is scarcely possible in the absence of laboratory experience; without such experience 0.88 or ten times this amount has little or no meaning. Clinical benefit from the drug is readily appreciated by the patient. To the human with pain this drug has a known benefit. Therefore, we suggest that the *nitroglycerin unit* be established

as a measurement for drugs and for other methods of treatment. For example, another drug which we measured has 1.5 nitroglycerin units and is effective for a longer period of time. Another form of treatment has 5 nitroglycerin units and these units are permanent in their action. These measurements together with those concerning the electrical condition in the heart should find a place in the new physiology of the disease because they concern effectiveness of therapy.

Conclusions

(1) The three factors in coronary heart disease that produce symptoms and kill are defined. While each of these factors is produced by changes in arterial inflow (produced by the disease), each has its own identity. Because this identity is now established, each of these factors can be investigated and appraised. We believe identification is a preliminary requirement for these accomplishments.

(2) The axiom of treatment is presented. Blood supply to ischemic muscle is the common denominator to all three factors but alterations in blood supply manifest themselves in these three different ways.

(3) For purpose of clarification it is suggested that the electrical effect be separated from the other two. If this is done then we believe that consideration involving inflow and muscle can be more readily understood, investigated, and appraised.

(4) The effect of nitroglycerin on blood supply was determined by direct measurement. This drug increases the amount of blood available to ischemic muscle by 0.88 cc per minute and is effective for 5 minutes.

(5) Because of common usage and the relief of pain following the use of nitroglycerin, it is suggested that the clinical results and the laboratory measurements be combined to form the *nitroglycerin unit* and that this unit be recognized as a measure for other drugs and also for surgical operation. For example, one drug under investigation has 1.5 nitroglycerin units and another form of therapy has 5 nitroglycerin units and these units are permanent.

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Comparison of the Cardiovascular Dynamics and the Size and Fat Content of the Heart in Lean and Fat Dogs*

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THE degree of adiposity is not only an important body variable but also one which can be varied to an important degree through dietary means. At either extreme significant pathologic effects are encountered, but even within the "physiologic range" adiposity has important influences. It affects the architecture of tissues, the size and function of organs, and the weight and operation of the body as a whole.

We have approached the study of adiposity through relatively long-term experiments on dogs. Our point of departure was the fact that there are obligatory relationships between the size of the body and the size and function of the heart. We attempted to distinguish between the effects of adiposity on body size and body weight. The circulatory effects due to differences in weight were held to a minimum by not allowing the dogs to exercise. Thus we were mainly concerned with the mass effects of a large as compared with a small amount of body fat.

The most striking finding was the extremely small effect on the heart and circulation caused by a large difference in adiposity. In short, it was found that the only measurable differences were that dogs who had lost over one-third their weight had a slightly smaller total blood volume and a slightly smaller cardiac silhouette than the controls. There were no other significant differences in cardiovascular dynamics. There were no significant group differences in the weight, fat, and protein content of the ventricular musculature.

PROCEDURE

Important factors as breed, sex, age, and physical activity of the animals were held constant while adiposity was varied through differential feeding. Ten three-year-old purebred female beagles were used. The dogs were numbered randomly from 1 to 10 and were divided into two groups according to whether their numbers were odd or even. From the time they were puppies they were kept in cages and never exercised. They lived in an air-conditioned room, followed a constant routine, and received good care. All had been used in a previous experiment which involved decompression to simulated high altitude, and in this connection dogs 2, 4, 5, and 8 had undergone splenectomy. After a control period, dogs with "odd" numbers were given horse meat in addition to their regular diet of Purina Dog Chow in an effort to increase their weight. This resulted in a loss of weight, and the meat was discontinued. Although the original diet was then restored *in luxus*, only one dog exceeded the initial weight by the end of the experiment. This indicated the initial weight was near the maximum, and they were referred to as "fat" dogs, as indeed they were. The dogs in the other group were given a diet adequate in every respect except in total calories. They slowly lost weight and were thereafter referred to as "lean" dogs. The dogs were sacrificed 10 months after the differential feeding was begun. The only procedure throughout this period that in-

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TABLE I

Mean Body Weight and Heart Area ± the Standard Error

Weeks	Fat dogs		Lean dogs	
	kg	sq cm	kg	sq cm
0	11.8 ± 0.68	38.3 ± 0.79	11.8 ± 0.68	37.6 ± 0.71
16	10.8 ± 1.2	38.0 ± 1.9	8.66 ± 1.6	36.0 ± 1.4
20	10.7 ± 1.1	36.8 ± 1.7	7.85 ± 1.5	34.4 ± 1.7
27	10.6 ± 1.2	36.1 ± 0.75	7.16 ± 1.2	34.4 ± 1.7
32	11.4 ± 1.2	39.0 ± 1.0	7.26 ± 1.3	35.4 ± 1.2
39	11.4 ± 0.99	38.5 ± 1.1	7.39 ± 1.1	35.4 ± 2.3

terrupted their regular routine was the hemodynamic measurements carried out under light pentobarbital anesthesia.

Teleroentgenograms were obtained on three occasions before, and on five occasions during, the experimental feeding period. In each instance the dog was hooded and placed with the anterior chest wall in contact with a specially constructed cassette holder and Bucky grid. Posteroanterior views were taken at 70 kv, 100 ma with the tube at a distance of 2 meters and an exposure time of 0.5 sec. Two sets of films were obtained ordinarily on each dog, but occasionally only one was of good quality. Heart areas were measured with a Keuffel and Esser compensating polar planimeter, Model 4236 M. Duplicate measurements on each film agreed within 0.2 sq cm. The mean between the values from the two films was taken as the reading for any one occasion.

Cardiac output and plasma volume measurements were made after six months of the experimental period utilizing the classic dye dilution principle.[1] The dogs were anesthetized with pentobarbital sodium (1 ml 6.5 per cent solution/5 lb body weight) administered intraperitoneally. A known quantity of T-1824 was quickly administered into the right jugular vein and serial femoral arterial blood samples were collected at 2-sec intervals for 30 sec. Additional samples were obtained at 3, 4, 5, and 6 min. Analysis of these samples for T-1824 and the subsequent construction of time concentration curves permitted the computation of cardiac output, plasma volume and other parameters of cardiovascular function.[2]

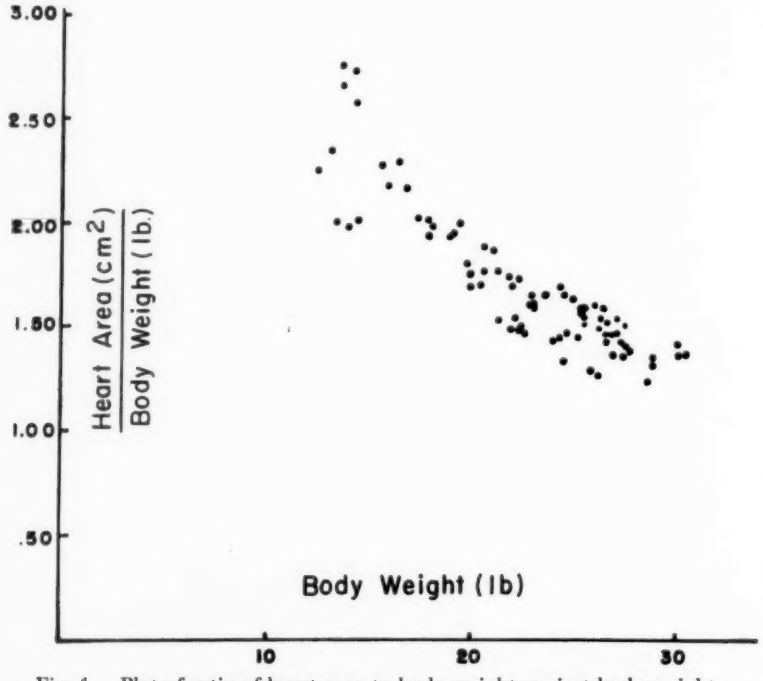

Fig. 1. Plot of ratio of heart area to body weight against body weight.

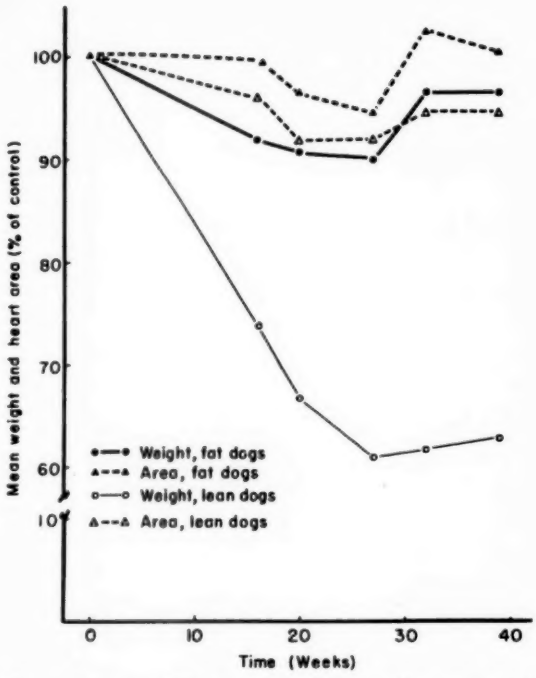

Fig. 2. Group differences in mean cardiac area and body weight of fat and lean dogs expressed as per cent change from control values.

One day after the last roentgenograms were obtained, the dogs were sacrificed and their hearts removed and quick-frozen. Later they were thawed slowly, and the ventricles were stripped of all tissue above the atrioventricular groove and of any external accumulation of fat over the ventricles proper. The ventricles and all extraventricular tissue were weighed separately. The ventricular mass was homogenized in a blender. The water content was determined by adding acetone to a weighed sample in a flask which was then dried with nitrogen at 40° C.[3] Fat content was determined on the residuum by extraction with chloroform-methanol.[4] Noncollagenous nitrogen content was determined using the method of Lilienthal *et al.*[5] All determinations were run in duplicate.

Results

During the control period, the mean weight of the dogs to be designated as "fat" was 11.8 kg ± 0.68 kg (Table I). During the next 27 weeks on an unrestricted diet, the weight of the fat dogs decreased to 10.6 ± 1.2 kg (89.6 per cent of original weight) and then rose in the next five weeks to 11.4 ± 1.2 kg (96.2 per cent of original weight), which they maintained until the end of the experiment. The dogs on restricted rations lost weight steadily, reaching a minimum weight of 7.16 ± 1.2 kg (60.8 per cent of original weight) after 27 weeks and then gained slightly to 7.39 ± 1.1 kg (62.7 per cent of original weight) when the experiment was terminated. It is obvious that some factor was operating on all of the dogs resulting in a common tendency toward variations in body weight. For this reason group differences in body weight as well as absolute change in weight were taken into account.

Cardiac Silhouette

The roentgenologic findings are summarized in Table I and Figures 1 and 2. Figure 1 is a plot of the ratio of heart area to body weight against body weight. The ratio varies inversely with weight because the cardiac area remains relatively constant. Despite the scattering of individual values, a uniform trend is discernible, indicating that the dogs behaved as a single group in this important respect.

Figure 2 shows group differences in mean cardiac area and body weight expressed as per cent change from control values. A comparison of the curves depicting cardiac area shows a common pattern of change with slightly smaller values for the lean group. When these differences were subjected to decremental analysis, it was found that only the first measurements in the experimental period showed a significant difference. In other words, the only significant decrease in heart size observed in the lean group occurred in the first 17 weeks, indicating that a longer time was not required for the heart area to decrease as a result of loss in body weight.

Cardiovascular Dynamics

The results of the hemodynamic studies are summarized in Table II. The outstanding finding is the fact that there was no difference in the absolute values for any of the items listed except that whole blood volume was smaller in the lean dogs. This 15 per cent difference was not proportional to the decrease in weight, which was at that time 39 per cent. When whole blood volume, plasma volume, central plasma volume, and cardiac output were expressed in terms of body weight, the values were, of course, all significantly higher in the lean dogs.

TABLE II

Measurements of Cardiovascular Status Six Months after Differential Feeding Began

	Fat dogs (5)		Lean dogs (5)
	Mean ± S.E.	"t"	Mean ± S.E.
Weight, kg	11.5 ± 0.6	5.36*	7.0 ± 0.6
Hematocrit, %	43.7 ± 2.6	1.44	39.4 ± 1.4
Plasma volume			
(a) ml/kg	40.1 ± 1.2	3.90*	62.2 ± 5.6
(b) ml	463 ± 29	1.34	423 ± 7
Blood volume			
(a) ml/kg	71.6 ± 1.7	3.66*	102.5 ± 8.3
(b) ml	826	2.43*	700 ± 19
"Central" plasma volume			
(a) ml/kg	5.9 ± 0.8	5.92*	13.0 ± 0.9
(b) ml	68 ± 9	1.63	92 ± 12
Cardiac output			
(a) ml/kg/min	66.3 ± 9.2	4.37*	156.6 ± 18.5
(b) ml/min	777 ± 134	1.40	1134 ± 216
Heart rate/min	170 ± 8	0.82	162 ± 6
Stroke volume, ml/beat	4.8 ± 1.2	1.20	7.1 ± 1.5
Blood pressure, mm Hg	120 ± 8	1.06	130 ± 5
PVR†, dynes sec cm^{-5}	15185 ± 1875	0.86	12454 ± 2540
Mean circulation time, sec	5.6 ± 0.7	0.37	5.2 ± 0.6

* Statistically significant: $P < 0.05$; $t = 2.31$.

† Peripheral vascular resistance.

S. E. = Standard error.

TABLE III

Chemical Analyses of Ventricular Muscle at End of Experiment*

No.	Body weight, kg	Heart weight (g)			Composition of ventricles		
		Extra-ventricular tissues	Ventricular mass	Total	% Water	% Fat	μg N_2/ml
Fat dogs							
1	12.52	24.5	53.4	77.9	74.5	3.9	186
3	11.65	12.8	60.5	73.3	74.85	4.6	217
5	9.93	19.1	46.2	65.3	72.35	5.3	251
7	11.98	15.9	60.4	76.3	73.1	4.1	218
9	10.88	15.6	46.8	62.4	74.0	4.55	220
Mean	11.38	17.6	53.5	71.1	73.8	4.5	218.4 (13.6% protein)
Lean dogs							
2	8.84	21.0	52.5	73.5	74.9	4.45	171
4	7.66	12.7	63.4	76.1	73.85	3.45	229
6	6.53	13.9	55.1	69.0	73.75	4.6	215
8	7.89	16.3	42.5	58.8	73.95	4.65	200
10	6.07	10.3	42.0	52.3	75.1	3.6	226
Mean	7.39	14.8	51.1	65.9	74.3	4.2	209.8 (13.1% protein)

* All values mean of two determinations.

COMPOSITION OF VENTRICULAR MUSCULATURE

Table III summarizes the results of the chemical analyses. Insignificant differences were found in the water content and noncollagenous nitrogen.

Discussion

The differences in body weight between the fat and lean dogs represented extremes between forced feeding, on the one hand, and undernutrition, on the other. Nevertheless, under the conditions of our experiments, these differences were remarkable more for lack of effects on the heart and circulation than for the small changes produced. At the time of sacrifice there was an insignificant difference in absolute mean ventricular weight between the fat and the lean dogs. Thus, unless it is assumed that at the beginning of the experiment the mean ventricular weight was greater in the lean group, it is evident that the loss of body weight did not affect ventricular weight. This assumption is supported by the similarity of the water, fat, and noncollagenous protein content of the ventricular musculature in the two groups. Our findings are in accord with the concept that, in the absence of malnutrition, the weight of the ventricular musculature remains constant despite great differences in body weight.

The slight decrease in cardiac area in the lean dogs as measured from the roentgenograms must be explained on some basis other than difference in ventricular weight. One possibility is the smaller amount of "extra-ventricular tissue" in the lean compared with the fat dogs. The difference was 16 per cent by weight and was obvious on gross examination. Another possibility which might account for the decrease in cardiac area observed was the change in blood volume. Although the blood volume per kilogram was greater in the lean than in the fat dogs, the absolute volume was less, and this might well have been a significant factor. This explanation would accord with the findings of Sjöstrand, Kjellberg, and Rudhe,[6,7] who found a close correlation in healthy persons between blood volume and cardiac volume during rest. They found that the volume of blood is distributed according to rule, with approximately 10 per cent in the heart, 20 per cent in the lungs, and 70 per cent in the systemic circuit. Consequently, changes in absolute amount of blood volume are reflected in the size of the heart, which is one-third to two-thirds blood and the rest muscle.

Interesting to note in connection with our findings are the observations of Keys and his co-workers,[8] who reported a decrease in heart volume of about 20 per cent for 32 men on semistarvation rations. Keys[9] stated, "In general, a loss of 30 per cent in body weight is associated with a loss of about 20 per cent in heart weight." The conclusion was reached that the heart is not much more resistant to undernutrition than are other tissues. Although our findings are not to be compared directly with theirs, the implication is clear that there is a great distinction between the effects of malnutrition and starvation and a loss of weight (mainly adiposity). We are in complete agreement that there is much more to learn concerning the relationship between nutritional states and cardiovascular disease.

It is clear that the size of the heart as determined from teleroentgenograms has limited meaning until it is related to other factors. Recently, an item analysis was carried out to determine the relative significance of such variables as age, sex, height, and body weight, and characteristics of the thoracic cage, including height of the diaphragm, internal transverse diameter, and anteroposterior dimension for predicting "standard values" for heart size in man.[10] When these items were arranged in order of significance, it was found that measurements related to the thoracic cage had lower significance than those related to general bodily characteristics and that the single most important relationship was that between heart size and body weight. It is important to learn to what extent this relationship is also valid for ventricular mass.

Summary and Conclusions

By differential feeding within the limits of good health, 5 out of 10 purebred beagles eventually lost over one-third of their weight. Associated with the weight loss there was a

slight decrease in cardiac area in the lean dogs as measured from the teleroentgenograms. This was explicable by the reduction of blood volume and the decrease in the amount of fatty tissue around the heart. Postmortem studies revealed insignificant differences in the weight of the ventricles and in the percentages of water, fat and non-collagenous protein in the fat and lean dogs.

The important implications are the relatively small effect either of considerable adiposity of long duration or of its absence on the ventricular mass and composition. More studies are needed on the relationship between nutritional status and its influence on the heart.

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New Methods

Transseptal Left Atrial Puncture

New Technique for the Measurement of Left Atrial Pressure in Man*

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LEFT HEART catheterization has become a well-recognized and indispensable diagnostic method in the assessment of patients with acquired or congenital heart disease. It has also permitted the conduct of many physiologic studies impossible before safe methods for obtaining left heart pressures were available. In the continuing search for improved diagnostic methods carried out at the National Heart Institute, transseptal left heart catheterization was recently evaluated in experimental animals.[1,2] In this technique the left atrium is punctured by means of a retractable needle introduced through a cardiac catheter, the tip of which is positioned against the interatrial septum. Experimentally, the method was found to be both practical and safe, and it has recently been applied in our catheterization laboratory. The present report describes these initial clinical experiences.

TECHNIQUE OF CATHETERIZATION

Fourteen transseptal left atrial punctures were successfully performed in 13 patients. All of them had predominant or isolated mitral valve disease. In 10 patients the major lesion was considered to be mitral stenosis, and in 3 mitral regurgitation. Five had previously undergone mitral commissurotomy. One patient was studied before and after operation. In 10 patients, left ventricular pressure was measured simultaneously with left atrial pressure by anterior transthoracic puncture of the left ventricle.[3] All pressures were recorded with Statham P23D pressure transducers and a multichannel cathode ray oscillograph. Nitrous oxide tests for the detection of left-to-right shunts[4] with right ventricular sampling were performed in 9 patients before and after the transseptal puncture. All patients were premedicated with pentobarbital 100 mg.

Catheterization was performed with the patient supine on a fluoroscopic table. Under local anesthesia, the right or left saphenous vein was exposed, a cardiac catheter inserted, and right heart catheterization carried out. This catheter was then withdrawn and a shortened, 59.5 cm, #8 Cournand catheter with a removable hub was passed and its tip positioned in the right atrium near the fossa ovalis. The hub of the catheter was removed, and a specially constructed 19-gauge needle, 61 cm in length and curved at its distal end (Fig. 1) was then passed through the lumen of the catheter. The needle was allowed to rotate freely during its passage and was inserted until its point lay just within the catheter tip. The metal indicator arrow attached to the proximal end of the needle was then rotated until the point was directed posteriorly and medially. Under fluoroscopic

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control, the catheter and needle were advanced together until resistance was encountered at the interatrial septum. With the catheter held stationary, the needle was then pushed forward its remaining length of 15 mm through the interatrial septum and into the left atrium (Fig. 2). The position of the needle was verified by visual comparison of blood samples obtained from two atria as well as by the pressure pulse observed on the oscilloscopic screen.

Results

In the 13 patients in whom entry into the left atrium was achieved, the initial puncture was successful. Arrhythmias at the time of puncture were not observed. During the entire procedure the patients gave evidence of no more discomfort than that ordinarily experienced during right heart catheterization. In two additional patients, both with grossly enlarged right atria, the left atrium could not be entered, and right heart catheterization alone was performed. No complications were observed in any patient during or following the procedure.

The right ventricular nitrous oxide tests performed immediately before and after septal puncture were all negative.[4]

A typical left atrial pressure pulse contour recorded through the needle in a patient with mitral stenosis is shown in Figure 3. The simultaneous left ventricular pressure was obtained by anterior thoracic puncture. In some patients, the needle was withdrawn from the left atrium, across the septum into the right atrium, as the pressure was recorded continuously. Such a tracing obtained in a patient with mitral insufficiency is reproduced in Figure 4.

Comment

The transseptal method of left atrial puncture will undoubtedly prove to be a useful alternative to the methods of left heart catheterization presently employed. It permits both right and left heart pressure measurements to be carried out in the course of a single study, and the patient can easily be maintained in a steady basal state. Although the saphenous vein is ligated after the catheter is removed, at least two studies are possible in each patient without extensive

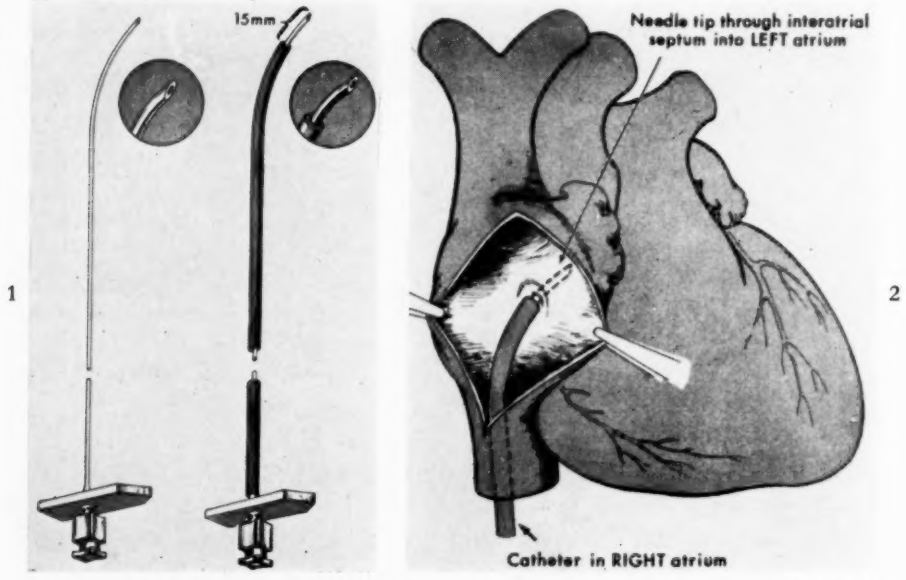
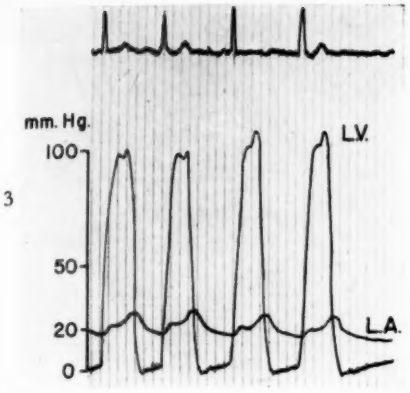


Fig. 1. (*Left*) Specially constructed 19-gauge needle employed in transseptal left atrial puncture. The metal arrow at the hub indicates the direction of needle curvature. (*Right*) The needle has been passed through a #8 cardiac catheter the hub of which has been removed.

Fig. 2. Diagrammatic representation of the position of the cardiac catheter and needle following puncture of the atrial septum.



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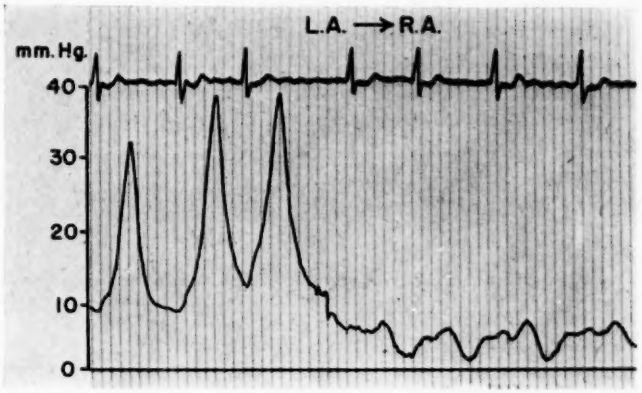

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Fig. 3. Simultaneous left atrial and left ventricular pressures obtained in a patient with mitral stenosis and atrial fibrillation. The left atrial pressure was obtained by transseptal puncture and the left ventricular pressure by percutaneous puncture through the anterior chest wall.

Fig. 4. Pressure tracing obtained as the needle was withdrawn from the left atrium (*L. A.*) across the interatrial septum into the right atrium (*R. A.*) in a patient with mitral regurgitation.

dissection. The effects of exercise can be determined by pedaling of the ergometer with the opposite leg. The ultimate safety of the technique and the frequency with which the left atrium may be entered must be determined by further clinical studies.

Preliminary experiences with a 17-gauge needle indicate that the left ventricle and aorta may be catheterized by a second smaller catheter passed through it. The experimental studies have also indicated that the larger needle may provide a useful route for selective left atrial angiocardiography.

Summary

A new method for the measurement of left atrial pressure in man is described. In 13 patients the interatrial septum was punctured by means of a flexible needle passed through a cardiac catheter which had been introduced from the saphenous vein and positioned with its tip against the fossa ovalis. No complications were observed after the procedures. The advantages of the technique and its present and projected usefulness are discussed.

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Review

Etiology and Pathogenesis of Syndromes Associated with Periarteritis Nodosa Lesions

A Unified Theory*

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In 1755, Matani[1] described nodules upon small arteries. Similar lesions were again described by von Rokitansky[2] in 1852. However, these pathologic changes were not related to specific clinical signs until Kussmaul and Maier's paper in 1866.[3] They presented "an undescribed, unusual disease of the arteries (periarteritis nodosa), accompanied by Bright's disease and a rapidly progressive generalized paralysis of the muscles." Their patient was a 27-year-old white man who suddenly became ill. He showed a mild fever, muscular weakness and tenderness, paresthesias and progressive emaciation. During the course of his illness, he developed low back pain, intermittent colicky abdominal pain, subcutaneous pea-sized nodules, and a progressive widespread paralysis, marked by exacerbations and remissions. His urine showed albuminuria and hematuria. He died four months after the onset of his illness. Postmortem examination showed nodular thickening of numerous arteries of the caliber of the hepatic artery or smaller. The diseased arteries were found in the heart, kidneys, gastrointestinal tract, liver, subcutaneous tissues, and voluntary muscles. Ferrari[4] later suggested that this syndrome be described by the term "polyarteritis nodosa" because all three layers of the arteries were involved.

Since this report, more than 500 cases have been described. However, the term "periarteritis nodosa," or "polyarteritis nodosa" has gradually been used for various groups of patients, some of whom differ greatly from the patient of Kussmaul and Maier. At the present time, there is controversy about (a) the pathologic criteria for the diagnosis of periarteritis nodosa, and (b) about the pathogenesis and etiology of the condition. For example, the term "periarteritis nodosa" has been used to describe some patients with malignant hypertension,[5,6] patients showing hypersensitivity to sulfonamides and other drugs,[7–10] patients with Wegener's syndrome,[11,12] Cogan's syndrome,[13,14] some rheumatoid arthritis patients, particularly those who had received cortisone,[15] temporal arteritis patients,[16] and animals who have been made hypertensive by means of various procedures which injure the kidneys[6,17,18] or by means of kidney injury plus the administration of anterior pituitary and adrenal cortical extracts.[19]

We shall first describe the pathologic criteria of periarteritis nodosa lesions. Then we shall describe their pathogenesis, and how various etiologic agents can produce periarteritis nodosa lesions by means of common biochemical and physiologic reactions.

PATHOLOGIC CRITERIA OF PERIARTERITIS NODOSA LESIONS

Three types of pathologic lesions have been described:

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(1) *Lesions of Muscular Arteries:* The first type of lesions corresponds to the pathologic changes found in Kussmaul and Maier's patient. The pathologic changes occur in small and medium-sized arteries of the muscular type, near the hila of viscera, in striated muscles and near peripheral nerves. They are common in bifurcations and branchings of the arteries, especially in the wall of the gastrointestinal tract, near the mesenteric attachment, and in the pancreas and kidneys. The lesions are usually absent in the pulmonary but not the bronchial arteries, and in the splenic follicular arterioles. Microscopic examination shows the lesions to be of various ages. Nodules and small aneurysms are common.

(2) *Microscopic Arteriolar Lesions:* The second type of lesion shows only microscopic pathologic signs, namely fibrinoid necrosis and inflammation of all three layers of the arterial walls. However, the lesions have a different distribution from lesions of the first type. For example, in this type, arterioles, venules, capillaries, as well as small arteries are involved. Lesions are usually found in the heart and kidneys, in the pulmonary vessels (pulmonary as well as bronchial arteries) and in the splenic follicular arterioles, but are not common in the pancreas and gastrointestinal tract. Also, the lesions all appear to be of the same age. For this reason, Zeek[20] has described these lesions by the term "hypersensitivity angiitis" rather than "periarteritis nodosa." She believes that lesions of the first type are related to hypertension, whereas lesions of this second type are related to hypersensitivity.

Other investigators[21,22] have not been able to make such a sharp distinction between these two types of lesions. A case of Berblinger's[23] illustrates this. A 61-year-old man injured his finger. Three weeks later he showed signs of tetanus and was given tetanus antitoxin. Ten days later he developed a generalized rash, which slowly disappeared in two weeks. However, a few days later he suddenly developed shock and died. At autopsy, periarteritis nodosa lesions of the muscular arteries of the liver, kidneys, prostate, testicle, and adrenals were found. There were no lesions in the lungs, spleen, and central nervous system. Death was due to rupture of a necrotic renal artery. In this case, the lesions were of the first type, even though they were due to hypersensitivity to tetanus antitoxin.

(3) *Extravascular Lesions:* In the third type of lesion, there are widely dispersed extravascular lesions in the lungs and other organs, in addition to vascular lesions of the first or second type. The extravascular lesions are characterized by an inflammatory exudate rich in eosinophils, necrosis of the exudate, and severe alterations of collagen fibers with a granulomatous (epithelioid or giant cell) reaction.[22,79]

We believe that these three types of lesions represent variations of a common biochemical and physiologic mechanism rather than separate entities. However, we do not believe that the term "periarteritis nodosa" should be used for patients showing changes described by the term "temporal arteritis" or "cranial arteritis." In these latter cases, elastic as well as muscular arteries are involved, and the arteritis shows a characteristic giant-cell infiltration.[24]

Pathogenesis and Etiology of Periarteritis Nodosa Lesions

We believe that the pathologic changes described by the term "periarteritis nodosa" are due to one basic factor, namely, intraarterial (or intravascular) edema and necrosis. This causes the inflammatory exudate which is characteristic of periarteritis nodosa lesions Observations by Arkin[25] support this concept. He described the development of periarteritis nodosa lesions in four stages:

(1) *The Edematous or Degeneration Stage:* There is edema and a thready, fibrinous exudate about the elastica interna of the affected artery. Swelling and separation of the arterial (or arteriolar) muscle cells by the exudate occur. In the smaller arteries, that is, those without vasa vasorum, these changes occur chiefly in the innermost media, in the subendothelial region. In the larger arteries, that is, those with vasa vasorum, the changes appear more often in the outer media, lying near the elastica externa. However, careful study shows that the changes begin in areas near the vasa vasorum, or the smaller branches of the artery.

A part or the entire circumference of the arterial wall may undergo coagulation necrosis, with a hyaline-like appearance of the inner media. The endothelium may also be affected so that the cells become desquamated or disappear over the affected area. The subendothelial changes, the edema, and the fibrinous exudate may elevate the endothelium, causing it to bulge into the lumen of the artery, even reducing the lumen to a narrow slit.

(2) *The Acute Inflammatory Stage:* Leukocytes begin to wander into the necrotic area. These are mostly polymorphs. However, many eosinophils may be present, along with lymphocytes and plasma cells. The fibrinous exudate may extend from the intima to the adventitia, with distortion of the inner media. The elastica interna becomes stretched and fragmented. The perivascular connective tissue becomes edematous and infiltrated. Thrombosis of the artery may occur. Toward the end of this stage, aneurysm formation or rupture of the artery may occur.

(3). *The Granulation-Tissue Stage:* Proliferation of fibroblasts occurs from the adventitia into the inflammatory zone. There is a decrease in polymorphs and an increased number of lymphocytes and plasma cells. Cellular granulation tissue, rich in fibroblasts and new capillaries, replaces the fibrin network and the hyaline necrotic area.

(4) *The Healed Granulation-Tissue Stage:* A fibrous scar forms. The arterial channel may be thrombosed or recanalization may occur.

The mechanism by which intraarterial and intravascular edema and necrosis occur is shown in Figure 1. As shown, periarteritis nodosa lesions can appear in two different groups of patients.

Group I Patients: Hypertension and Injury to the Kidneys

Here, the production of periarteritis nodosa lesions depends primarily on the secretion of large quantities of aldosterone, which produces the intraarterial edema. This leads to necrosis of the cells of the vessel wall and is followed by the typical inflammatory exudate.

It is well known that increased aldosterone secretion occurs in patients with severe essential hypertension and with malignant hypertension.[26,27] Furthermore, it has been shown that aldosterone causes an increased water and sodium concentration and a decreased potassium concentration of the arterial walls and muscles of hypertensive patients.[28] However, this alone will not produce the pathologic signs of periarteritis nodosa. Another factor is necessary, namely, injury to the kidneys. As has been pointed out elsewhere, we believe that one of the metabolic functions of the kidneys is to inactivate aldosterone.[26] Therefore, when injury to the kidneys is present, the aldosterone produced during the course of the normal daily metabolic activity accumulates in the body.

We believe that this is the explanation for the presence of periarteritis nodosa lesions in the following conditions:

(1) *Malignant Hypertension:* In 1931, Klemperer and Otani[5] found pathologic changes similar to those of periarteritis nodosa in two

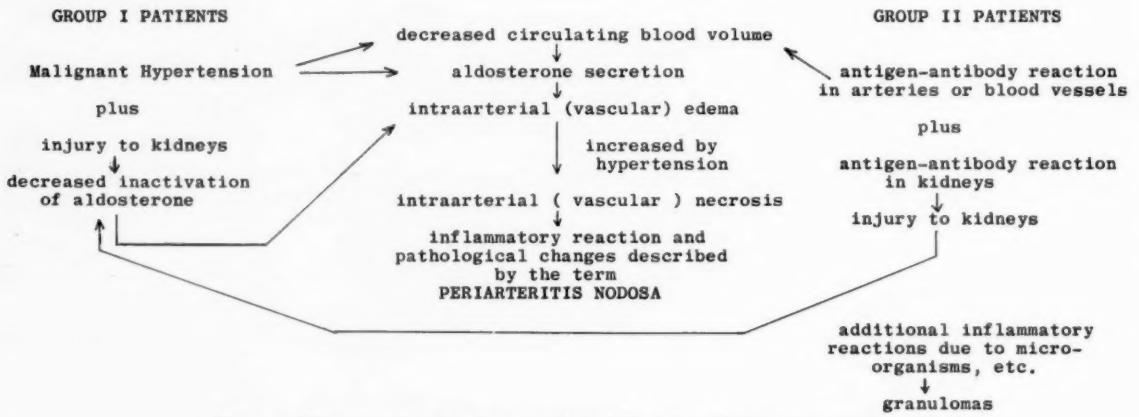

Fig. 1. Diagram showing how periarteritis nodosa lesions are produced.

cases of malignant hypertension. Other physicians have had similar experience. Zeek-Minning[29] has pointed out that the periarteritis lesions usually occur terminally in such cases, in association with hypertension and severe renal disease; and the patients usually die of these conditions before a fatal periarteritis nodosa lesion, such as a ruptured aneurysm, can occur. In such cases, the most typical lesions are probably missed frequently at autopsy, because sections are not taken routinely from the sites where periarteritis nodosa lesions usually begin, for example, the sites of mesenteric attachments to the intestines, the vasculature at the neck of the gallbladder, and the hilar regions of other abdominal viscera. Zeek-Minning examined more than 100 cases of severe hypertension and renal disease and found periarteritis nodosa lesions in about one-fourth of these cases.

(2) *Experimental Procedures Which Cause Hypertension and Injure the Kidneys:* In animals, periarteritis nodosa lesions have been produced by a variety of experimental procedures associated with the development of hypertension and injury to the kidneys. The most common procedures have included some degree of interference with the vascular supply of one or both kidneys, but not sufficiently to cause massive infarction of the kidneys. For example, mechanical measures, such as applying clamps or ligatures to the renal arteries, or wrapping the kidneys in silk, cotton or cellophane[6,17,18] have been successful. In these experiments, periarteritis nodosa lesions occurred in some but not all of the animals used. The lesions have been found most commonly in the mesenteric and pancreatic arteries, but may be widespread, except that the pulmonary arteries are not affected.[18]

For example, Goldblatt[30] produced permanent hypertension in dogs, similar to human essential or malignant hypertension, by bilaterally partially constricting the renal arteries, and by other similar procedures. In a few of the dogs, he found periarteritis nodosa lesions. In 1939, Wilson and Byrom[6] produced malignant hypertension in rats by compressing the renal artery with a silver clip. Acute arteriolar necrosis occurred. In addition, lesions that closely resembled those of periarteritis nodosa were found in the mesentery. In 1940, Grant[31] reviewed the subject of periarteritis nodosa. He also re-examined the microscopic sections from Wilson and Byrom's experiments and confirmed the similarity between the arterial lesions experimentally produced in rats to those found in humans. Similar experimental observations have been made by Smith, Zeek and McGuire,[32] Loomis[17] and others.

Nonmechanical methods which cause hypertension and injury to the kidneys can also cause periarteritis nodosa lesions. Ham[33] fed rats either a single massive dose of activated ergosterol or a diet rich in calcium, phosphorus, and phosphoric acid. This caused widespread calcification of the kidney vessels. Most of the animals lived six months or more and developed hypertension. At autopsy, they showed signs of severe injury to the kidneys. In addition, more than half the animals showed also periarteritis nodosa lesions in the intestinal arteries.

(3) *Experimental Injury to the Kidneys and the Administration of Anterior Pituitary and Adrenal Cortical Mineralocorticoid Hormones:* This method was first described by Selye and Pentz.[19] They gave rats an overdosage of desoxycorticosterone acetate (DOCA) after removing one kidney. The animals developed severe hypertension and periarteritis nodosa lesions. Selye[34] also produced similar pathologic changes in rats by using large doses of crude extracts of the anterior pituitary gland or by somatotrophic anterior pituitary hormone. These observations have been confirmed by Masson and his co-workers,[35] by Mellgren[36] and others. Selye and others[37] have also shown that continuous exposure to a nonspecific injurious agent, such as cold, can cause hypertension and periarteritis nodosa lesions in unilaterally nephrectomized rats which were fed on a diet high in sodium chloride and protein.

(4) *Experimental Removal of the Kidneys:* Hypertension and periarteritis nodosa lesions have also been produced in rats in whom both kidneys have been removed.[20] This type of hypertension is called renoprival hypertension or "post-nephrectomy hypertension," and has been discussed previously.[26]

(5) *Periarteritis Nodosa Lesions Limited to the*

Pulmonary Arteries: Cases of periarteritis nodosa lesions limited to the branches of the pulmonary artery have been described in cases in which there is also pulmonary hypertension. Although Parker and Weiss[38] found no true angiitis in their series of cases of mitral stenosis with chronic passive congestion of the lungs, they did find five examples of pulmonary arteriolar necrosis simulating the systemic lesions of malignant hypertension. More recently, typical pathologic findings of periarteritis nodosa lesions limited to the pulmonary circulation have been reported by Old and Russell[39] in a case of Eisenmenger's complex; by Hultgren[40] in cases of patent ductus arteriosus with pulmonary hypertension; by Symmers[41] in one case of mitral stenosis and one case of chronic cor pulmonale of unknown etiology; by Spain[42] in cases of severe mitral stenosis with pulmonary hypertension; by McKeown[43] who found four instances in 111 cases of cor pulmonale collected from a series of 6770 autopsies; and by Braunstein[44] who described six cases—three cases of advanced mitral stenosis, one case of atrial septal defect, and one case of pulmonary hypertension due to multiple thrombotic occlusions of the small pulmonary arteries.

The above physicians have called attention to the presence of pulmonary hypertension in their patients. However, they have not recognized the significance of the fact that almost all if not all of these cases of pulmonary periarteritis nodosa had severe congestive heart failure. In other words, pulmonary hypertension alone is not enough to produce periarteritis nodosa lesions. There must be present another factor, namely, excessive aldosterone secretion. In these cases, the aldosterone secretion was probably caused by the congestive heart failure. (Renal injury, if present, could also cause retention of aldosterone.) However, most of the case reports of periarteritis nodosa limited to the pulmonary arteries do not describe changes in the kidneys. In several of Braunstein's[44] cases, glomerulonephritis or congestion of the kidneys was present.

Group II Patients: Hypersensitivity States Involving Antigen-Antibody Reactions

It is well known that antigen-antibody reactions are frequently associated with an edematous and inflammatory reaction.[53] Therefore, if an antigen-antibody reaction occurs with an antigen which is localized in the arteries or other blood vessels, intraarterial edema will occur. However, this alone is not enough to produce periarteritis nodosa lesions.

Only a small percentage of animals or patients who develop antigen-antibody reactions show the pathologic signs of periarteritis nodosa lesions. The developments of such lesions in these patients depends on three, and possibly five factors:

(a) *The intensity of the antigen-antibody reaction* in the blood vessels and the subsequent intravascular edema and necrosis.

(b) *Injury to the kidneys* by the antigen-antibody reaction and the accumulation of aldosterone, due to the inability of the injured kidneys to inactivate it.

(c) *The secretion of aldosterone* as a result of the antigen-antibody reaction. Aikawa[54] has studied the volume of body fluid in which sodium ion is diluted by injecting a known amount of radioactive sodium intravenously and determining its concentration in the serum three hours later. He found in two rheumatic fever patients values of 46.3 and 36.8 per cent of the body weight. Neither patient had clinically demonstrable edema. In other patients, values higher than 30 per cent of the body weight were invariably associated with clinical edema. He interpreted these high values in rheumatic fever patients as a sign of an abnormal increase in the permeability of cell membranes. This alteration in body fluid can cause a decreased circulating blood volume, just as occurs in congestive heart failure, and may also be associated with an increased secretion of aldosterone.

(d) A fourth factor may be present as a result of an antigen-antibody reaction which injures the kidneys. The decreased inactivation of aldosterone may cause not only intraarterial edema, but also a very *severe hypertension.* This in turn can cause further injury to the kidneys and thereby cause further inactivation of aldosterone. In this way, a vicious cycle is created and perpetuated.

(e) It is also possible that a fifth factor, *a host*

factor, may also be responsible for the development of periarteritis nodosa lesions after an antigen-antibody reaction. Such a host may develop an inflammatory reaction which is more severe than normal, or may be a hypersecretor of aldosterone, even though the usual clinical signs of primary aldosteronism are not present.

The concept that the periarteritis nodosa lesions are due to hypersensitivity developed in the following way: In 1925, Gruber[45] suggested that the periarteritis nodosa lesions might represent a general sensitivity reaction to a variety of infectious and toxic agents which acted upon the arteries, rather than the result of any one specific etiologic agent. In 1930, Klinge[46] produced lesions in rabbits by repeated injections of horse serum. Some of these lesions resembled periarteritis nodosa lesions. In 1937, Clark and Kaplan[47] described two fatal cases of serum sickness and pointed out the similarities between the lesions in their patients and rheumatic fever and periarteritis nodosa lesions. In 1942, Rich[48] described similar lesions not only in serum sickness patients, but in patients who showed hypersensitivity to sulfonamides. In 1943, he and Gregory[49] gave normal rabbits a single intravenous injection of a large quantity of horse serum. "Acute diffuse glomerulonephritis" developed in seven out of nine rabbits. In addition, lesions in the arterioles, capillaries and in the small muscular arteries of various organs developed in some of the rabbits, which Rich and Gregory considered to be periarteritis nodosa lesions. These observations could not be confirmed by Fox and Jones,[50] nor by Smith and Zeek,[51] but have been confirmed by Orbison.[55] Since the publication of Rich's observations, numerous reports have appeared of patients who showed similar pathologic signs, as a result of hypersensitivity to sulfonamides,[7] thiourea,[9] Dilantin,[8] iodine,[10] antisyphilitic arsenical compounds,[52] etc.

According to Rose and Spencer[22] periarteritis nodosa lesions due to hypersensitivity and antigen-antibody reactions can be divided into two main groups:

(1) *Patients with Periarteritis Nodosa Lesions, without Pulmonary Parenchymatous Lesions:* In many of these patients, no etiologic agent can be found to explain the development of the periarteritis nodosa lesions. Specific bacterial agents, such as streptococci,[22] gonococci, meningococci, tubercle bacilli, treponema, viruses, etc., all have been suggested as etiologic agents. More recently, Reimann and his associates[56] described similarities between trichinosis and periarteritis nodosa patients. In addition, many periarteritis nodosa patients show a positive reaction to the trichinella precipitin test. However, when the more specific trichinella complement fixation test is used, the incidence of positive reactions in periarteritis nodosa patients decreases greatly.[57]

It is interesting to speculate on the reason why some periarteritis nodosa patients show lesions limited to the small muscular arteries, whereas others also show lesions in veins and capillaries. This may depend on the nature of the antigen, on the size of the antigen-antibody precipitate, or on the nature of the cells in the blood vessels to which different antigens attach. In addition, lymph vessels are found only in the adventitial layer of the blood vessels. Therefore, if an antigen-antibody reaction occurs near the endothelium, the antigen-antibody precipitate may be trapped in a large muscular artery, whereas it may be able to pass through a smaller vessel, or be carried away by the lymphatics of a smaller vessel. One cannot be certain that this is so, until one can identify the etiologic agent.

(2) *Patients with Periarteritis Nodosa Lesions, Associated with Pulmonary Parenchymatous Lesions:* Mönckeberg[58] described a patient who showed periarteritis nodosa lesions in the lungs. In 1923, Ophüls[59] described a second case with pulmonary involvement. In addition, this case showed numerous other unusual signs, such as extensive involvement of the veins, as well as involvement of the small pulmonary arteries, eosinophilic infiltration of the bronchi and lung tissue, and granulomatous lesions of the serous membranes. Since this report, numerous other cases have been described of pulmonary parenchymatous and granulomatous lesions in various organs in association with the usual periarteritis nodosa lesions.

Rose and Spencer[22] have pointed out that

when the lung tissue is involved in association with periarteritis nodosa lesions, the patients may show the following signs:

(a) Bronchial asthma is a common symptom.

(b) The branches of the pulmonary artery are often involved, as well as the bronchial arteries.

(c) Unusual caseous or granulomatous lesions are often found, particularly in the lungs, but also in other viscera.

(d) The arterial lesions tend to be distinctive and show numerous eosinophils in the acute stage, and a granular reaction, sometimes with giant cells, in the healing stage.

(e) Marked eosinophilia is a common finding.

Wegener's Granulomatosis: When granulomatous lesions are present, they may produce the following distinctive syndrome: In 1931, Klinger[60] described a patient with destructive sinusitis, nephritis, and uremia, in whom, at autopsy, periarteritis nodosa lesions, splenic granulomata, and glomerular lesions were also found. Wegener[11] later reported three additional cases. Since nasal and paranasal lesions were predominant in his cases, he called the condition "rhinogenic granuloma." This syndrome of necrotizing granulomatous lesion, in the upper or lower respiratory tract (nose, sinuses, nasopharynx, trachea, bronchi, lungs, or adjacent areas), generalized periarteritis nodosa lesions, involving both arteries and veins, almost always in the lungs, and more or less widely disseminated in other viscera, and a glomerulitis, characterized by necrosis and thrombosis of loops or lobes of the capillary tuft, capsular adhesion, and granulomatous lesions, is now generally known as "Wegener's granulomatosis."[12]

Other Clinical Conditions Associated with Periarteritis Nodosa Lesions

(1) *Rheumatoid Arthritis:* Although it has been stated that vascular lesions do not occur in rheumatoid arthritis patients,[61] there have been numerous reports recently in which vascular lesions have been described. The lesions which have been found can be divided into four groups:

(a) Perivascular or adventitial accumulation of leukocytes, plasma cells, and other cells, without noticeable necrosis.[62]

(b) Subacute arteritis, manifested by infiltration of lymphocytes and histiocytes through all layers of the vessel wall, and possibly some exudation of fibrin and swelling of collagen, but again, without severe necrosis.[63]

(c) Lesions of acute arteritis with infiltration of polymorphs and other types of leukocytes, and necrosis of the vessel wall. However, the lesions are limited to one or two organs, such as joints, heart, subcutaneous nodules, etc.[64,68]

(d) Generalized periarteritis nodosa lesions.[65]

It has been observed that a high percentage of rheumatoid arthritis patients who show periarteritis nodosa lesions have received ACTH or corticosteroid therapy.[62,68] There has been no adequate explanation why corticosteroid therapy should induce or aggravate periarteritis nodosa lesions in rheumatoid arthritis patients. It has been shown that cortisone can have a detrimental effect on blood vessels in two experimental conditions: (a) Thomas[66] has shown that cortisone favors the development of the generalized Shwartzman reaction in rabbits after the injection of meningococcic endotoxin; (b) focal ectasia and occlusion of glomerular capillaries develop in rabbits treated with cortisone.[67]

We should like to present another explanation for this phenomenon: It is known that ACTH and the corticosteroids decrease the inflammatory reaction of the host to bacterial or viral invasion and allow bacteria and viruses and other microorganisms, particularly intracellular organisms, to multiply and spread in the host. In addition, the steroids have no effect on antibody formation in humans.

Elsewhere, we have pointed out[69] that the etiology of rheumatic fever is the result of two simultaneous processes: (a) a reinfection with a group A streptococcus of the same serologic type which previously had caused infection, and (b) a specific antigen-antibody reaction, similar to, but not identical with, that which occurs in serum sickness, which results from the reliberation of type specific streptococcal M protein into the systemic circulation. We believe that rheumatoid arthritis has a similar *double* etiology, namely, a reinfection with a pleuropneumonia-like organism (PPLO) and

a specific antigen-antibody reaction, which results from the reliberation of PPLO antigen into the systemic circulation.[70] If ACTH or the corticosteroids are given to such patients, the inflammatory reaction is decreased, but the PPLO (which are intracellular) continue to multiply and form antigen. In this way, antibody production and an antigen-antibody reaction continue in the blood vessels. The result is frequently widespread periarteritis nodosa lesions.

In this connection, it is interesting to note that ACTH and the corticosteroids have been used in the treatment of periarteritis nodosa patients. Results have been variable. Baggenstoss, Shick, and Polley[71] treated two patients; despite initial improvement, both patients died of cardiac and renal failure. At autopsy, there was apparently complete healing of the arterial lesions. All histologic signs of inflammation had disappeared within three weeks in the first case, and within three months in the second case. However, in the process of healing, fibrous obliteration of the arterial lumina had occurred, resulting in infarcts which were particularly numerous in the kidneys, heart, and intestinal tract. Ehrenreich[72] had a similar experience. However, a more recent report by Pickering and his associates[73] indicates that the steroids may prolong life in periarteritis nodosa patients.

The beneficial effects of ACTH and the corticosteroids in these periarteritis nodosa patients may be due to the fact that they suppressed the inflammatory reaction subsequent to an antigen-antibody reaction. However, in these cases, the agent responsible for the presence of antigen in the body was probably not capable of multiplying and of forming new antigen during the period of steroid administration.

(2) *Cogan's Syndrome:* In 1945, Cogan[74] described four patients who showed a granular interstitial keratitis and vestibular and auditory symptoms, such as vertigo, tinnitus, and nystagmus, and who usually developed complete deafness. The only systemic signs he found were an increased white blood count and an eosinophilia. In 1953, Olina and his associates[13] described the case of a 23-year-old woman who developed periarteritis nodosa lesions after two attacks of interstitial keratitis with vestibular and auditory symptoms. In 1956, Crawford[14] described two additional patients with Cogan's syndrome who also developed periarteritis nodosa lesions.

All three patients had received ACTH or corticosteroids. We believe that the mechanism of development of periarteritis nodosa lesions in these patients is similar to that which occurs in the rheumatoid arthritis patients. The etiologic agent responsible for Cogan's syndrome is not known. Rosen[75] has suggested that it might represent a postvaccinal encephalitis.

Periarteritis Nodosa Lesions Occurring Spontaneously in Animals

Although periarteritis nodosa lesions have been produced experimentally in animals, the lesions have been found to occur spontaneously. Wilens and Sproul[76] found periarteritis nodosa lesions in 47 out of 487 rats older than two years, which had spent their lives in a laboratory and had been untreated except for being on a restricted diet of dried milk and powdered ground wheat. However, these rats were not healthy and 19 had overt renal disease. Measurements of blood pressure were not done.

Periarteritis nodosa lesions have also been found in other animals. Lüpke[77] found nodular vascular lesions in a 10-year-old axis deer that had died in a public park in Ludwigsburg, Germany. Within a year, 12 other deer from the same herd died with similar pathologic changes; and within a decade, the herd of 100 previously healthy animals had diminished to eight. Axis deer in the zoological gardens of Hamburg, Germany, and Calcutta, India, did not show these findings. Periarteritis nodosa lesions have also been described in the pig, the calf, and the dog.[78] The cause of the periarteritis nodosa lesions in these animals is not known.

Conclusions

The term "periarteritis nodosa," or "polyarteritis nodosa," does not refer to a disease. Instead, it represents a more or less homogeneous

group of pathologic signs, characterized by fibrinoid necrosis and inflammation of all three layers of the arterial (and other vascular) walls. In many cases, only the small muscular arteries are involved. In other cases, arterioles, veins, and capillaries are also involved. In still other cases with pulmonary parenchymal involvement, extravascular granulomas also occur.

These pathologic changes can be caused by numerous unrelated etiologic agents. However, they are all associated with common biochemical and physiologic changes, which cause intraarterial (and intravascular) edema and necrosis and the secretion of aldosterone.

Patients with periarteritis nodosa lesions can be classified into three main groups:

Group I. Periarteritis Nodosa Lesions Associated with Malignant Hypertension and Injury to the Kidneys: The hypertension causes intraarterial edema and aldosterone secretion. The renal injury prevents inactivation of aldosterone and aggravates the hypertension. This group includes:

(1) Malignant hypertension patients.

(2) Animals in whom malignant hypertension has been induced by injury to the kidneys.

(3) Animals in whom malignant hypertension has been induced by injury to the kidneys, and who, in addition, have received anterior pituitary hormones or adrenal mineralocorticoid hormones such as desoxycorticosterone (which has an aldosterone-like effect).

(4) Patients with periarteritis nodosa lesions localized to the pulmonary arteries. These patients have pulmonary hypertension, which causes localized intraarterial edema of the pulmonary arteries. Aldosterone secretion occurs because of the congestive heart failure, which is present; or if concomitant injury to the kidneys is present, renal inactivation of aldosterone is prevented.

Group II. Periarteritis Nodosa Lesions Associated with Hypersensitivity and Intraarterial (or Intravascular) Antigen-Antibody Reactions: The intravascular antigen-antibody reaction causes intravascular edema and necrosis. Aldosterone secretion can occur in one of the following ways: the antigen-antibody reaction, which causes changes in cell permeability and a decrease in circulating blood volume; injury to the kidneys due to a local antigen-antibody reaction; hypertension developing as a result of kidney injury and decreased inactivation of aldosterone. This in turn causes further aldosterone secretion, further kidney injury and further inactivation of aldosterone; and finally, a host factor may be present—the host may be a hypersecretor of aldosterone.

These patients may be divided into two main subgroups:

(A) Patients with periarteritis nodosa lesions without pulmonary parenchymal involvement. These patients show the typical signs described by Kussmaul and Maier, namely, nonspecific signs such as fever, weakness, anemia, leukocytosis, and local signs due to arterial occlusions affecting various organ systems, such as the heart, kidneys, muscles, central nervous system and peripheral nerves, skin, gastrointestinal tract, liver, gallbladder, etc.

(B) Patients with periarteritis nodosa lesions associated with pulmonary parenchymal involvement. In addition to the above signs, these patients frequently show bronchial asthma, clinical and x-ray signs of pulmonary infiltrations, a marked eosinophilia, and signs of granulomatous lesions in the kidneys, upper respiratory tract, and other organs.

Group III. Periarteritis Nodosa Lesions Occurring in Other Patients:

(1) Rheumatoid arthritis patients, especially those who have received ACTH or the corticosteroids.

(2) Cogan's syndrome patients, especially those who have received ACTH or the corticosteroids.

In this group of patients the corticosteroids apparently allow the microorganisms responsible for the rheumatoid arthritis and Cogan's syndrome to continue to multiply and form new antigens, thus accelerating the antigen-antibody reaction which leads to the periarteritis nodosa lesions.

Treatment: The therapy of patients with periarteritis nodosa patients is difficult. If the cause is malignant hypertension, the treatment should be directed to removing the cause of the hypertension. If the patient is hypersensitive to some antigen, ACTH or the corticosteroids may be life-saving. However, if

these drugs are used when extensive arterial lesions are already present, rapid healing may occur with fibrosis and occlusion of the affected blood vessels. This may cause further injury to the affected organs. If the kidneys are affected in this way, progressive malignant hypertension and death may occur. If a patient develops signs of periarteritis nodosa lesions while receiving steroid therapy for rheumatoid arthritis or Cogan's syndrome or Sjögren's syndrome, etc., the steroid therapy should be stopped.

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16

Seminar on Ballistocardiography*

Effects of Drugs on Ballistocardiographic Recordings

Correlation with Other Cardiovascular Measurements in the Dog and in Man†

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IN DETERMINING the cardiovascular effects of drugs, the need for a convenient clinical method has led several investigators to the use of ballistocardiography.[1–4] Most of these investigations have been concerned primarily with the drug-elicited changes in cardiac output as measured by the ballistocardiograph. However, Hamilton *et al.*[5] concluded that the amplitude of the ballistocardiogram was more closely related to the velocity of ejection than to the quantity of blood ejected. Starr and others related the amplitude and contour of the ballistocardiographic complexes to the rate of application of simulated heart force in cadavers.[6–8] In addition, several investigators have shown that ballistocardiographic amplitude is greatly reduced but not completely eliminated by occluding the venous return to the heart or by preventing the ejection of blood by the heart. These investigators have concluded that the amplitude of the ballistocardiogram is largely determined by the forces involved in the movement of blood.[9–11]

Several methods have evolved for obtaining records of the body movements occurring with each heart beat. Notably, these are the Starr table (a high-frequency system), the ultra-low-frequency system, and the direct-body method. The physics of these systems and the artefacts in their records have been described[12–14] and have been discussed also by others in this Seminar. However, for the purpose of evaluating the acute influence of drugs on the human cardiovascular system some of the advantages of the direct-body method might be pointed out here: (1) Direct-body recordings are easily obtained without discomfort to the subject. (2) They may be obtained from the patient confined to the hospital bed. (3) The low cost of installation of the equipment permits the use of direct-body units in the physician's office.

Based on the above considerations, studies were instituted in this laboratory to investigate the applicability of ballistocardiography as a clinical method of evaluating acute drug-produced changes in myocardial contractility.[15–19] The general plan of these investigations has been

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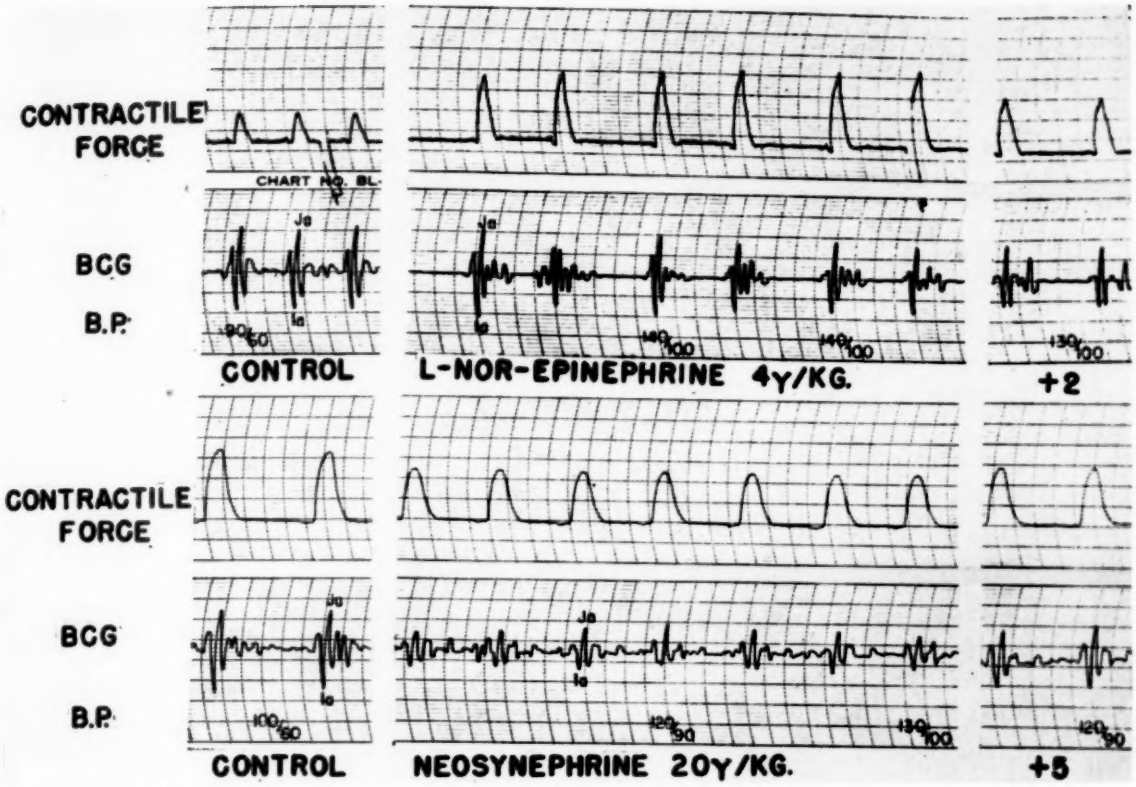

Fig. 1. Effects of *l*-norepinephrine and Neo-Synephrine on cardiac contractile force, BCG, and blood pressure. Synchronous recordings in closed-chest anesthetized dog; right ventricular contractile force recorded by the strain-gauge arch method; the incision for implantation of arch was made 2 days prior to the experiment. Anesthesia: morphine 3 mg/kg and urethane 1 gm/kg. Time intervals 0.2 sec with each vertical line. The amplitude and slope changes in the I_a-J_a wave elicited by Neo-Synephrine were markedly greater than those elicited by *l*-norepinephrine (Levophed), although the diastolic pressure increments were similar. The systolic pressure changes elicited by *l*-norepinephrine were 20 mm Hg greater than those produced by Neo-Synephrine and, correspondingly, the pulse pressure was also greater.

to adapt clinical ballistocardiographic methods (direct-body and ULF) so that they may be used on the dog. With such preparations it has been possible to observe and compare the acute changes in the ballistocardiogram produced by drugs with directly measured changes in heart contractile force, pressures and contours of the aortic pulse recording, and the electrocardiogram. A comparison was made of such findings with ballistocardiographic, blood pressure, and electrocardiographic changes produced by the same drugs in the normal human subject and the patient undergoing therapy.

The results of these studies have led to the following conclusions: The changes in the I_a wave depth and the slope of the I_a-J_a wave seem to have a direct relationship to the acute drug-elicited changes in the force of ejection. An inverse relation between the amplitude of the I_a-J_a wave and drug-produced changes in peripheral resistance has been observed.

These conclusions were drawn largely from animal experiments in which ventricular contractile force and aortic pulse pressures were obtained synchronously with direct-body and ULF acceleration ballistocardiograms. Cotten and Bay[20] have shown from direct measurements of left ventricular contractile force that there is a direct relationship between the degree of force occurring prior to the beginning of ejection and the diastolic pressure. Cotten and Maling[21] have also shown that if diastolic pressure is maintained constant there is a direct relationship between the stroke volume and the total amount of force occurring with each systole. Peterson[22] has shown that much of the force which is ap-

plied to the blood mass during the ejection phase of the cardiac cycle as kinetic energy is lost to overcoming peripheral resistance, to aortic distention, and to frictional forces. Since forces involved in the movement of blood largely determine the ballistocardiogram, the drug-elicited changes in these factors will largely determine the amplitude and contour of the ballistocardiogram recorded during the drug response.

Methods of Study

The data used in reaching the foregoing conclusions were obtained from experiments in which the following drugs were used as tools to vary cardiac force and peripheral resistance: phenylephrine (Neo-Synephrine), which increases peripheral resistance without increasing myocardial contractility;[23,24] epinephrine (Suprarenin) and *l*-arterenol (Levophed), which increase peripheral resistance and myocardial contractility;[23–25] nitroglycerin, which decreases peripheral resistance;[17,26] and isoproterenol (Isuprel), which decreases peripheral resistance and increases myocardial contractility.[15,17,26]

Doses were usually in the range which produced heart force increments of about 100 per cent or arterial pressure changes of about 40 mm Hg. These intravenous doses expressed in μg/kg of body weight of the dog were: phenylephrine, 10 to 20; epinephrine and arterenol, 1.0 to 4.0; isoproterenol, 0.5 to 1.0; nitroglycerin, 50 to 100. Phenylephrine (10 mg/L), epinephrine and arterenol (4 mg/L) were administered to the human by intravenous infusions. Nitroglycerin and isoproterenol were administered sublingually. The changes in the ballistocardiograms elicited by these agents were closely comparable for the dog and human so long as some minor qualifications are regarded.

Phenylephrine (Neo-Synephrine): Vasoconstriction

Direct-body acceleration recordings following phenylephrine were characterized by a decrease in the depth of the I_a wave, a decrease in the amplitude and slope of the I_a-J_a wave and an increase in the early diastolic waves[17,18,27,28] (Fig. 1). The ULF recordings were generally similar, although the decrease in the depth of the I_a wave was more pronounced and the amplitude changes were not as great. These changes were accompanied by the following changes in cardiovascular dynamics: a moderate increase in diastolic pressure, a slight increase in systolic pressure, a decrease in pulse pressure, and little change in the intrinsic force of contraction of the cardiac muscle. There was usually a decrease in heart rate.

The pulse pressure contour changes resembled those described by Alexander[29] and by Peterson[30] under conditions of an increase in peripheral resistance without an increase in myocardial contractility. The increase in diastolic pressure without an increase in the force of contraction of the myocardium would result in a greater portion of the force of contraction occurring during the pre-ejection phase of the cardiac cycle than occurred in the control period prior to drug administration. This would reduce the force available to move blood during the ejection phase. The increase in peripheral resistance would tend to further prevent the movement of blood. More force would be stored in the aortic wall at this higher diastolic pressure level. Such changes could account for the observed reduction in the amplitude and slope of the ballistocardiographic waves during systole and the increase in the numbers of early diastolic waves.

Nitroglycerin: Vasodilation

With nitroglycerin there was generally an increase in the depth of the I_a wave and an increase in the amplitude of the I_a-J_a wave with a slight increase in the slope of this segment[17,18,31–33] (Fig. 2). These direct-body ballistocardiogram changes were similar to the changes which occurred in the ULF recordings. The quantitative differences were largely those of a greater increase in the depth of the I_a wave for comparable changes in diastolic pressure.

At the dose level used, the decrease in diastolic pressure was usually marked. The decrease in systolic pressure was moderate to slight. The maximum systolic pressure was reached early in systole and there was a marked fall in pressure prior to the closure of the aortic valves. There was an increase in heart rate and a moderate reflex (sympatho-adrenal) increase in heart force. Under these conditions less force was required to raise the intraventricular blood mass to the

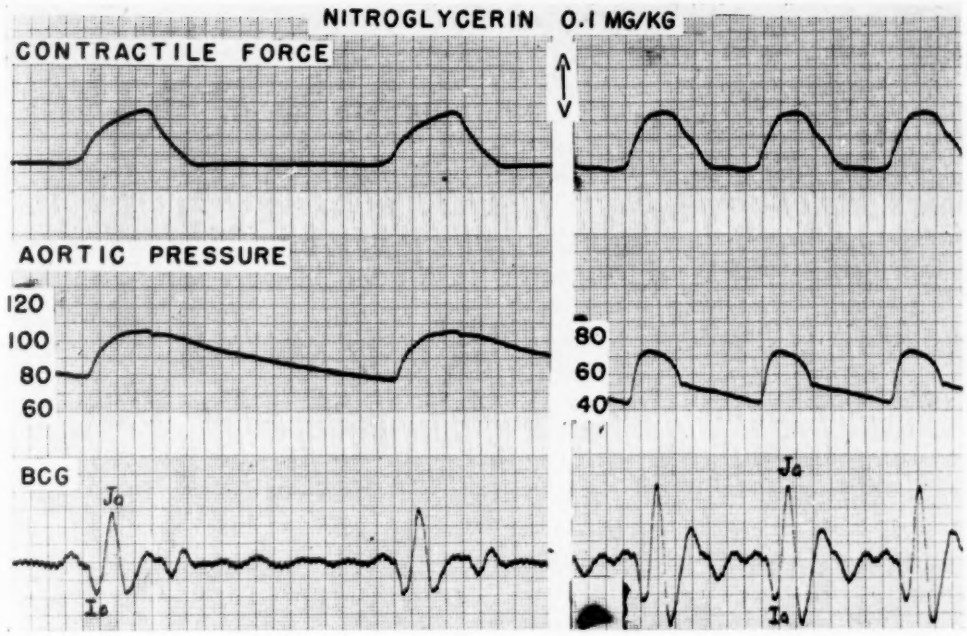

Fig. 2. Effects of nitroglycerin on cardiac contractile force, aortic pressure, and BCG. Conditions essentially as in Fig. 1. The decrease in diastolic pressure elicited by nitroglycerin was accompanied by a prominent increase in both slope and amplitude of the aortic pressure contour and a corresponding increase in ballistocardiographic amplitude. The rapid rise in aortic pressure during the initial ejection phase (acceleration transient) emphasizes the relationship between velocity of ejection and ballistocardiographic amplitude. Time interval between the heavy vertical lines is 0.1 sec.

low diastolic pressure level; therefore, more force was available to move blood during the ejection phase. The vasodilation resulted in a reduction in the resistance to flow and less force was stored in the aortic wall. These increments in velocity of ejection were reflected in the changes in the ballistocardiogram.

Isoproterenol (Isuprel): Vasodilation with Myocardial Stimulation

With isoproterenol there was a marked increase in the amplitude and slope of the I_a-J_a wave and an increase in the depth of the I_a wave.[15,17,18,34] The amplitude and slope changes were greater with this amine than with any other agent. Isoproterenol elicited a marked increase in force of cardiac contraction. This increment was accompanied by a decrease in diastolic pressure and usually a slight increase in systolic pressure resulting in a marked increment in pulse pressure. There was an accompanying increase in heart rate.

The force occurring during the pre-ejection phase of the cardiac cycle was reduced by the influence of the drug on diastolic pressure. The increase in total cardiac force greatly increased the force available to move blood during the ejection phase. The vasodilation greatly reduced the resistance to flow; therefore, these additive changes in the force of contraction and resistance to ejection resulted in a marked increase in the velocity of ejection and, correspondingly, a marked increase in the amplitude of the ballistocardiogram and slope of the waves.

Arterenol (Levophed): Vasoconstriction with Myocardial Stimulation

Since increments in cardiac force tend to increase the amplitude of the I_a-J_a wave, and increases in peripheral resistance tend to decrease the amplitude of this wave, the change in amplitude elicited by *l*-arterenol was largely dependent upon the preponderance of influence from either cardiac force or peripheral resistance.[1,16–18,28,35] In general, with a moderate increase in diastolic pressure (30–50 mm Hg), the depth of the I_a wave was reduced and the slope of the I_a-J_a wave was increased (see Fig. 1).

The changes in the ULF ballistocardiogram were similar to those reported for the direct-body recordings. However, the depth of the I_a wave was markedly shortened by this agent, and with comparable doses the decrease in amplitude was not as great as that usually seen in the direct-body recording. In each case the increase in the slope of the I_a-J_a wave was prominent.

The measured changes in hemodynamics elicited by arterenol were a marked increase in myocardial contractility, an increase in diastolic pressure with a more marked increase in systolic pressure, resulting in an increase in pulse pressure. The maximum ejection pressure was reached late in systole near the time of the closure of the aortic valves. The increase in diastolic pressure would result in an increase in the cardiac force occurring during the pre-ejection phase. However, with the increase in total contractile force there would be considerable force available to move blood during the ejection phase. There would be a high resistance to the movement of blood produced by the vasoconstriction and more force would be stored in the aortic wall during systole.

One can readily see why there could be an increase in cardiac force without an increase in ballistocardiographic amplitude or possibly a slight reduction in ballistocardiographic amplitude during the period of action of this agent. However, there was never a decrease in amplitude as great as that seen with phenylephrine during comparable diastolic pressure changes. In the patient with cardiogenic shock, *l*-arterenol elicited an increase in the amplitude and slope of the I_a-J_a wave of the direct-body records concomitant with the elevation of blood pressure from the hypotensive levels.[18,28]

Epinephrine

With epinephrine the results in the dog were closely similar to those reported for arterenol. In the normal human subject, the blood pressure and ballistocardiographic changes were more similar to those reported for isoproterenol. There was usually a slight decrease in diastolic pressure (5 to 10 mm Hg). The systolic pressure increased from 5 to 15 mm Hg. These changes resulted in an average increase in pulse pressure of 10 to 20 mm Hg. The increase in heart force without a concomitant increase in peripheral resistance in the human would result in a greater stroke volume and velocity of ejection. These changes were reflected in the increase in ballistocardiographic amplitude and in the increased slope of the I_a-J_a wave.

Digitalis

Studies of the effects of digitalis preparations in normal subjects and in patients with varying degrees of congestive failure have used the ballistocardiogram as a measure of stroke volume and cardiac output.[36–40] From these measurements the influence of the drug on the force of contraction of the heart was deduced. It is interesting to note that the most pronounced changes in the ballistocardiograms have been obtained from patients regarded as having marked congestive failure.[39] In the experimental animal with a nonfailing heart, the results with a number of digitalis preparations have been variable. Usually in the animal with good changes in myocardial contractility (increments of 100 per cent of control values) the ballistocardiogram increased slightly in amplitude.[19] The slope of the I_a-J_a wave increased. This increase in slope was usually the most prominent change in contour. There was an increase in diastolic and systolic pressure occurring concomitantly with change in contractility.

A recent publication by Cotten and Stopp[41] may aid in evaluating the changes in the ballistocardiogram observed in the normal subject and in the patient with congestive heart failure. These investigators have shown that the following hemodynamic effects accompany the increase in myocardial contractility elicited by digitalis preparations in the nonfailing heart: an increase in arterial pressure, an increase in peripheral resistance, a reduction in stroke volume, and a decrease in left atrial pressure. However, if left atrial pressure is maintained in the normal dog there is an increase in stroke volume concomitant with the increase in myocardial contractility. Large amounts of blood are required to maintain left atrial pressure in these animals, an observation which indicates a peripheral pooling of blood. The increase in peripheral resistance and decrease in stroke volume could be expected to mask the effects of an in-

crease in myocardial contractility as observed on the ballistocardiogram. Van Lingen *et al.*[39] observed the greatest increases in stroke volume and cardiac output as determined from the ballistocardiogram in the group of patients with a high right atrial pressure. Similar determinations in a group of patients with a lower right atrial pressure failed to produce the marked ballistocardiographic changes associated with increased stroke volume and cardiac output.

It has been our experience that the results with digitalis preparations depend largely on the state of the animal and time in the experiments in which they were given. The results are very much like those described for *l*-arterenol. However, the changes in the slope of the I_a-J_a wave have not been as striking with digitalis preparations and neither have the pressure changes.

Antihypertensive Drugs

The changes in the ballistocardiogram of the hypertensive patient observed following changes in blood pressure elicited by antihypertensive agents can be explained largely on the basis of the points outlined in this report.[42–46] Arbeit and Moret[40] have reported that a number of hypertensive patients fail to have normal ballistocardiograms after their blood pressure has returned to near normal levels. In many of these cases, administration of digitalis has converted the ballistocardiogram to normal. These investigators have also reported that in cases where the patient failed to respond to antihypertensive therapy, administration of digitalis often improved the ballistocardiogram of the hypertensive patient. Doses lower than the amount required for complete digitalization were often found adequate to produce normal ballistocardiograms.

Comments

In all cases, whether the recordings were obtained from a high-frequency table system, a low-frequency table system, or directly from the body, the marked changes in vascular dynamics elicited by these agents have resulted in comparable qualitative changes in the ballistocardiogram. An examination of the effects of changes in the range of recorded frequencies in the ballistocardiogram has shown that a low-frequency cut-off at near 5 cps with the subject on a ULF bed results in a ballistocardiogram similar to the direct-body recording.[19] Drug-elicited changes in these records are also closely similar to those recorded from the same subjects using the direct-body method. Changes in the slope of the I_a-J_a wave appear to be more indicative of changes in the force of ejection of the heart than mere changes in amplitude. With a low-frequency cut-off at 0.02 cps, increases in the force of ejection are usually reflected by an increase in both the slope and the amplitude of the I_a-J_a wave.

Drug-elicited increases in diastolic pressure have a tendency to shorten the I_a wave, while with the direct-body type of recording changes in diastolic pressure seem to be more reflected in the depth of the K_a wave. This is probably due to the phase changes which occur with rapid attenuation of the low frequencies elicited by the natural frequency of the body in the direct-body recordings and by the filter in the ULF recordings.

Summary and Conclusions

Variable ejection velocities have been produced in dogs and in human subjects by the administration of drugs with characteristically different effects on heart force and peripheral constriction. Ballistocardiographic tracings consistently exhibited an increase in amplitude and slope of the I_a-J_a wave when peripheral resistance was lowered or heart force was increased. Both of these latter changes are interpreted as increasing velocity of systolic ejection, as long as other circulatory parameters are unchanged.

The drugs used as test agents in these studies were: nitroglycerin, which produces vasodilation with little direct effect on heart force; phenylephrine, which produces vasoconstriction with relatively little effect on heart force; *l*-arterenol, which produces both vasoconstriction and an increase in heart force; epinephrine, which may or may not lower diastolic pressure but consistently increases heart force; and digitalis, which increases heart force with or without moderate increments in diastolic pressure.

With direct-body recordings, increments in diastolic pressure as with phenylephrine produced a decrease in amplitude and slope of the

I_a-J_a wave, a decrease in depth of the I_a wave, and an increase in the depth of the K_a wave. With ULF recordings an increase in diastolic pressure produced a decrease in the depth of the I_a wave and a reduction in the amplitude and slope of the I_a-J_a wave. Drugs such as nitroglycerin, which decrease diastolic pressure, caused an increase in the amplitude of this wave. When both diastolic pressure and force were increased there was usually little change in the amplitude of the ULF acceleration ballistocardiogram, although the slope of the I_a-J_a wave increased and there was a decrease in the depth of the I_a wave. Under the same conditions of change, direct-body recordings usually demonstrated a slight increase in slope and a slight reduction in amplitude of the I_a-J_a wave.

The influence of attenuation of low-frequency components on the drug-elicited changes in the ballistocardiogram and the associated phase shift are described.

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Reports on Therapy

Evaluation of Flumethiazide (Trifluoromethyl Thiazide) in the Outpatient Clinic*

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EDEMA is a common clinical problem, and constant attempts are made to refine methods of therapy. The use of oral diuretic agents has been a valuable addition to our therapeutic armamentarium. The recent introduction of chlorothiazide has made the problem of maintaining the edema-free state much easier in the ambulatory patient. Analogues of the basic compound always present the hope of being more effective than the parent compound. This report is our initial survey of the diuretic activity and toxicity in ambulatory cardiac patients of trifluoromethyl thiazide (flumethiazide).† The chemical structure of this drug is presented in Figure 1.

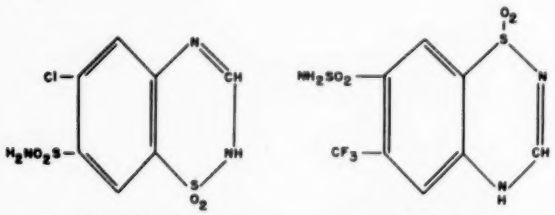

Fig. 1. Structural formulae, comparing chlorothiazide and flumethiazide.

METHODS AND MATERIALS

Acute-Response Studies: The acute diuretic response to this drug was determined by the weight loss experienced over a 48-hour period in 24 patients with cardiac failure. The patients were in a state of mild to moderately severe congestive heart failure and required a mercurial injection one to two times a week prior to this study. Each patient had been on a maintenance dose of digitalis which was continued. Diuretic therapy was withdrawn one to two weeks (depending on severity of heart failure) before the experimental drug was given but their other medication remained unchanged. The diet and salt intake was not well controlled since these patients were ambulatory and their economic status prevented a critical selection of food. The patients' ages ranged from 42 to 68 years and they were equally distributed between the sexes. The etiology of heart disease in this group of patients was predominantly arteriosclerosis. Several cases of chronic rheumatic valvular heart disease with associated coronary artery disease were also included. Only one patient had moderately severe and sustained hypertension.

The patients were weighed before breakfast and after voiding; the drug (flumethiazide) then was administered for two days, after which time they were weighed again. Doses of 400 mg twice a day, 800 mg twice a day, and 1,000 mg twice a day were employed. The weight response was also determined in the same manner for chlormerodrin (Neohydrin)‡ in a dose equivalent to 80 mg Hg and 500 mg and 1,000 mg of chlorothiazide (Diuril)§ given twice a day. At

* From the Department of Medicine, Hahnemann Medical College, Philadelphia, Pennsylvania.

† Furnished as Ademol by the Research Department of E. R. Squibb & Sons, New York.

‡ Furnished by Lakeside Laboratories, Inc., Milwaukee, Wisconsin.

§ Furnished by Merck Sharp & Dohme, Philadelphia, Pennsylvania.

TABLE I

Weight Response to Three Different Oral Diuretics

Patient		Chlorothiazide (Diuril) 500 mg b.i.d.[a]		Chlormerodrin (Neohydrin) 20 mg/Hg q.i.d.[b]		Flumethiazide Pho-18 800 mg b.i.d.		Flumethiazide Pho-18 1,000 mg b.i.d.		Flumethiazide Pho-18 1,000 mg t.i.d.[c]	
		Control	Drug	Control	Drug	Control	Drug	Control	Drug	Control	Drug
1	C. S.	133.8	132	135.3	132.5	137.5	136.5	139	135	136	134
2	M. M.	91.8	90.3	90.8	90.5	93.8	88	—	—	—	—
3	S. C.	111	108.3	110	108	112	110	112.5	111	—	—
4	N. Mc.	173	169.5	172	170.8	173	172.5	173	170	174	170.5
5	F. A.	146	148	146	148	149	150	152.5	147	148	148
6	E. C.	159.5	160.5	161	161	166	167.3	165	166.3	164	164.5
7	J. S.	164	162	165	164	—	—	—	—	166	163
8	A. P.	180	178	173.3	172	179	176	181	176.5	180	176
9	K. G.	133.5	131.8	134	132.8	136.8	137.3	—	—	—	—
10	N. L.	115	113.5	117.5	115.5	122.5	120	122	119	—	—
11	H. H.	143	141	144	142.5	143	140	—	—	144	142
12	L. H.	171	168	170	168	169	163	—	—	—	—
13	H. C.	109	106.3	—	—	—	—	—	—	—	—
14	J. E.	120	117	119	117	121	118	—	—	—	—
15	C. W.	173	170.5	173.8	168.5	—	—	—	—	—	—
16	M. W.	177	175	176	173	192.5	187.8	184	180	185	182.3
17	B. L.	163	161.8	164	163	168	165	167	163	—	—
18	H. C.	139	135	138	136	140.5	138.5	143.5	141	—	—
19	E. B.	97	95.3	99.5	97.8	96.5	95	96.5	95.5	—	—
20	L. S.	205	199	204	202	205	202.3	—	—	—	—
21	M. W.	153	149	150.8	148	155	152	156	153	155	151
22	M. P.	123.5	120	122.8	122.5	122.3	120	124.5	121.5	—	—
23	M. S.	173.5	170	173.5	171.3	166.5	165.4	—	—	169	165
24	G. F.	145	143	—	—	—	—	—	—	—	—
MEAN		145.8	143.5	147.3	145.7	147.5	145.2	147.4	144.5	162.1	159.6
P value <		0.001		0.001		0.001		0.001		0.001	

[a] B.i.d.—Twice a day, i.e. every 12 hours. [b] Q.i.d.—Four times a day, i.e. with meals and at bedtime.
[c] T.i.d.—Three times a day, i.e. every 8 hours.

least ten days elapsed without diuretic therapy between each dose of the drugs.

Chronic-Response Studies: The response to the chronic administration of flumethiazide was determined in 15 of the previously described 24 patients, plus 3 additional patients. The dosage was 2 Gm per day continuously for five weeks, and the patients were seen twice a week for review of clinical responses and evaluation of any side effects. Before the initiation of this study diuretic agents were withheld from these patients for a week so that the serum electrolytes stabilized. Serum electrolyte determinations included sodium, potassium, chlorides, and the CO_2 combining capacity. A complete blood count was done at the beginning and the end of the five-week period. Weights were recorded twice a week.

RESULTS

Acute-Response Study: The results of this study are summarized in Table I. Twenty-four patients received 500 mg of chlorothiazide (Diuril) twice a day, and 22 patients received 1,000 mg twice a day. The average weight loss at the end of two days was 2.3 pounds ($p < 0.001$) for the 500 mg dose and 2.9 pounds ($p < 0.001$) for the 1,000 mg dose. Twenty-two patients received chlormerodrin in a dose equivalent to 20 mg Hg four times a day and 1.6 pounds ($p < 0.001$) average weight loss resulted. For the 13 patients receiving 400 mg of flumethiazide twice a

day there were 1.4 pounds ($p < 0.01$) lost. The weight loss in 20 patients receiving 800 mg of flumethiazide twice a day was 2.2 pounds ($p < 0.001$) and 2.9 pounds ($p < 0.001$) in 13 patients receiving 1,000 mg twice a day. Ten patients lost an average of 2.5 pounds while receiving 1,000 mg of flumethiazide three times a day ($p < 0.001$).

There were no subjective or objective side reactions in this group of patients while taking the doses of flumethiazide as prescribed above. There was no apparent influence on the blood pressure; however, there was only one hypertensive patient in the group.

Chronic-Response Study: The results of this study are summarized in Table II. During the five-week period of continuous drug administration the 18 patients remained free of complaints due to congestive heart failure. Repeated physical examinations twice a week revealed that all patients were relatively free of findings of congestive heart failure and no mercurial duretics had

TABLE II

Effects on Blood Chemistry and Side Effects Resulting from Flumethiazide Administration Continuously for Five Weeks

Case			Weight	Blood chemistry								Side effects
				Na (meq/l)	K (meq/l)	CO_2 (meq/l)	Cl (meq/l)	BUN (mg %)	Hemoglobin (Gm)	Hematocrit	WBC	
1	C. S.	Control	138.5	143	5.2	21.6	100	22	11.6	40	5,300	None
		After drug	141.5	140	4.8	18.2	93	20	12	41	6,700	
2	M. M.	Control	93	144	3.9	24.9	92	12	12.6	42	7,400	None
		After drug	90.8	138	3.2	20.3	84	15	13	41	6,800	
3	S. C.	Control	112.5	148	4.7	19.1	101	13	14	48	10,800	None
		After drug	109	142	4.3	18	96	16	13	47	9,250	
4	N. Mc.	Control	174	136	3.9	18.6	86	16	14	48	9,800	Transient diarr hea, occas.
		After drug	172	142	4.8	23.7	94	12	14.8	48	8,100	ankle cramps
5	F. A.	Control	148.8	146	4.7	19.8	92	11	13.6	42	6,300	Weakness, 3rd week
		After drug	149	134	3.8	16	83	14	13	42	7,200	
8	A. P.	Control	144	142	4.3	24	100	14	13.2	43	7,200	None
		After drug	142	146	4.1	20	98	12	13	41	6,800	
9	K. G.	Control	140.5	144	4.4	26.6	86	14	13	41	9,600	None
		After drug	136.8	138	3.6	23.6	84	10	13.8	43	8,550	
10	N. L.	Control	122.3	140	4.6	23.3	89	23	12	41	9,600	None
		After drug	120.5	142	4.6	22	86	32	12.5	40	8,500	
16	M. W.	Control	186.3	144	5.4	25.7	96	10	12.8	43	5,450	None
		After drug	188	142	4.8	20.3	88	14	13	41	6,800	
17	B. L.	Control	166	139	5.9	17.4	100	29	10.8	35	6,560	None
		After drug	164	136	5.0	18	96	20	11	38	—	
18	H. C.	Control	144.5	138	4.2	22.9	94	17	10.6	36	5,200	Generalized pruritus (prev.
		After drug	145	134	3.8	20	90	21	11	35	5,600	history)
20	L. S.	Control	215.5	140	5.1	20.8	96	12	13.6	45	5,350	Pruritus of arms and back
		After drug	213.5	136	4.2	16.3	84	20	14	43	7,200	
21	M. W.	Control	157	148	5.0	24.1	100	8	12.6	42	7,850	Transient pruritus on back
		After drug	155	138	3.8	19.6	90	12	12.0	41	6,600	
22	M. P.	Control	126.5	141	4.6	22.5	100	14	11.8	38	5,300	None
		After drug	129	142	4.0	18.6	95	16	12	39	6,200	
23	M. S.	Control	169.3	140	4.2	20	94	18	12	40	9,600	None
		After drug	168.5	138	4.0	21	93	16	12.6	42	8,600	
	E. W.	Control	237	144	4.6	20.3	76	17	13	41	7,200	None
		After drug	238	140	4.0×	18	98	15	13	40	6,000	
	C. K.	Control	161.5	139	5.3	24.1	92	10	11.2	38	5,000	None
		After drug	159.8	140	4.0	18.2	86	15	11	38	7,800	
	A. G.	Control	112.5	145	4.0	20.4	87	10	15	51	9,400	None
		After drug	108	142	3.8	20	88	12	15	49	7,200	
Average		Control	152.8	142	4.7	22.0	93	15	12.6	42	7,300	
		After drug	151.6	139	4.1	19.5	90	16	12.7	42	7,288	

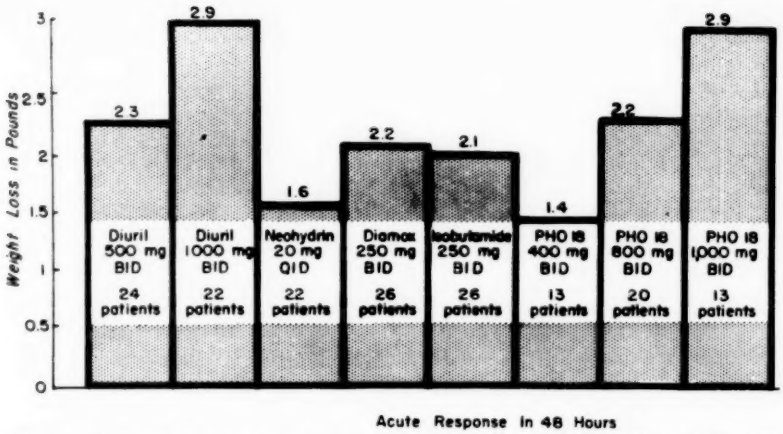

Fig. 2. Comparative potency (using weight response) of flumethiazide (Pho-18) and four other diuretics given orally.

to be administered. The average weight loss at the end of the five-week period was 1.2 pounds ($p < 0.01$). There was no apparent effect on blood pressure, but all patients were normotensive prior to therapy except one.

Side Effects: Five patients had complaints that were annoying during the study on flumethiazide. Pruritus was a major complaint in three. One patient had a generalized pruritus which he had experienced intermittently before the use of the flumethiazide and therefore this could not be necessarily attributed to this agent. Two patients experienced pruritus of the back and extensor surfaces of the arms and legs which stopped when the drug was withdrawn. A rash was not observed during the observation period. However, the administration of the drug was not prolonged beyond the five-week period to see whether a rash might have developed after persistent pruritic symptoms occurred.

One patient experienced marked weakness during the third week of the study. The complaint was transient and did not necessitate the stopping of the drug. Weakness is a rather common systemic complaint in patients with cardiac failure and is frequently difficult to attribute to the administration of the drug. However, the possibility of electrolyte depletion was not excluded as a factor at that time. One patient experienced transient diarrhea during the third week of the study but the diarrhea stopped in the presence of continued drug administration.

Laboratory Observations in Patients Receiving Flumethiazide for Five Weeks: A review of serum electrolytes at the beginning and end of this study showed a tendency for a decrease in the concentration of serum sodium, potassium, chloride, and CO_2. The change was minimal and there was no evidence of significant electrolyte depletion or imbalance at the end of the five-week period. The average sodium was 142 meq before and 139 meq after five weeks of drug administration. Potassium was 4.7 meq before and 4.1 meq after administration. Chlorides and CO_2 were 93 and 22 meq before, and 90 and 19.5 meq after the drug was given. There appeared to be no predominant effect on any one element. The blood urea nitrogen was not significantly influenced, nor were there any apparent changes in complete blood counts after five weeks of continuous administration of flumethiazide.

Comments

The comparative effectiveness, as determined by the acute response, of flumethiazide as a diuretic agent and other established diuretics can be seen in Figure 2. The response to the 800 mg dose of the agent under observation was equivalent to the response of a 500 mg dose of chlorothiazide in this group of patients. It would appear that the dose of flumethiazide would be larger than that of chlorothiazide for a similar weight response. Absorption from the gastrointestinal tract may be influencing this difference in response. However, when 2 Gm a day of chlorothiazide or flumethiazide were adminis-

tered, the acute weight response in this group of patients was the same. This is probably due to the fact that the maximum effective dose of each drug had been reached and further increase in dosage of either drug would not result in an increased weight loss.

The maximum effective dose of flumethiazide is apparently more potent than maximum effective doses of the carbonic anhydrase inhibitors acetazolamide (Diamox) and isobutamide, and of the oral mercurial chlormerodrin (Neohydrin).

A dose response curve of trifluoromethyl thiazide has been constructed as determined by the acute response to the four doses described in the acute response study (Fig. 3). Again it appears that a dose greater than 2 Gm a day does not have an increased diuretic effect when determined by weight response. This is also quite similar to the dose response curve of Diuril.[1]

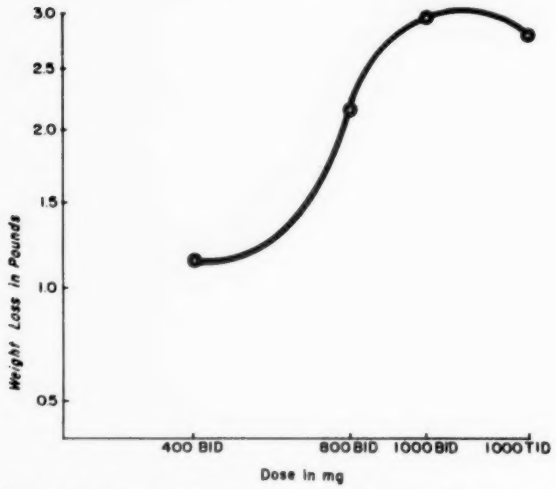

Fig. 3. Dose response curve to increasing doses of flumethiazide.

The chronic study of this agent revealed no major electrolyte or hematologic disturbances. The clinical response was quite favorable, and all patients maintained adequate cardiac compensation. The side effects, which were primarily pruritus, presented no major problem, but the possibility of rash if the drug had been continued has not been excluded.

Summary

(1) An acute and chronic diuretic response study with flumethiazide has been described.

(2) Flumethiazide is an effective diuretic agent as determined by weight response in ambulatory cardiac patients. An effective dose appears to be 800 mg which is equivalent to the diuretic activity of 500 mg of chlorothiazide.

(3) Doses of flumethiazide greater than 2 Gm a day had no more effect on weight loss in the group of patients studied than did the 2 Gm dose.

(4) Chronic administration of 2 Gm a day of flumethiazide maintained a group of cardiac patients free of congestive failure complaints. There was no significant influence on serum electrolytes or on the blood count.

(5) Side effects were minimal and consisted primarily of pruritus in 3 out of 18 patients. The pruritus stopped when the drug was withdrawn.

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Case Reports

Marfan's Syndrome*

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CASE PRESENTATION

A 43-YEAR-OLD Negro woman was transferred to Bellevue Hospital from another institution on October 18, 1955, with the diagnosis of rheumatic heart disease and a three-month history of progressive dyspnea and leg edema. The clinical findings included marked cardiac enlargement with a heaving apical impulse in the 5th intercostal space at the anterior axillary line and faint heart sounds. There was a loud, long, blowing diastolic murmur with a corresponding palpable thrill at the sternal end of the 2nd and 3rd right intercostal space and a loud systolic as well as a rumbling crescendo diastolic murmur at the apex. The pulse was regular at a rate of 130/min. The blood pressure was 160/40 mm. The liver extended two fingerbreadths below the costal margin. Marked pitting edema was present on both legs.

The initial impression of "rheumatic heart disease with mitral stenosis and insufficiency and aortic regurgitation" seemed supported by fluoroscopic and x-ray examination (Figs. 1 and 2). It showed the cardiac shadow considerably enlarged in all directions and the lower esophagus displaced backward, suggesting left atrial enlargement.

Extracardiac Findings Suggesting Marfan's Syndrome: The following extracardiac findings, however, pointed toward an etiologically and anatomically entirely different type of heart disease:

(1) The patient was unusually tall, 6 ft 4 in., very thin and long-limbed. Her features were masculine and appeared prematurely aged. Her fingers and toes were extremely thin, long and hyperextensible (Figs. 3 and 4). She had club feet that caused a limping gait.

(2) Her posture was stooped. The thorax showed a funnel-chest deformity with kyphoscoliosis of the dorsal spine, a prominent Ludwig's angle and a deeply depressed xiphoid process.

(3) She was blind. On the right eye the lens was dislocated temporosuperiorly and appeared opaque. On the left eye the lens was also opaque; the anterior chamber was shallow; and the pupil extremely miotic. (The patient had had poor vision since childhood and had become totally blind three years before admission.)

The peculiar body build and, more particularly, the association of "spider fingers" with ocular malformations suggested the diagnosis of arachnodactyly (Marfan's syndrome). These skeleto-ocular anomalies, in turn, indicated a specific, nonrheumatic etiology for the cardiac disease.

WHAT IS MARFAN'S SYNDROME?

In the course of its history there has been a continuous change in the emphasis on the various components which constitute Marfan's syndrome. When the French pediatrician Marfan[1] first described the syndrome in 1896, he stressed the *skeletal features:* the tall and lean build, the long, thin extremities and the spider-like fingers. Much later, attention was called to the association with congenital *anomalies of the*

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heart (Salle,[2] 1912) and congenital *dislocation of the lenses* (Boerger,[3] 1914). Only in 1943 did the serious potentialities of the syndrome become fully appreciated when the regular occurrence of *medial degeneration of the great vessels* was demonstrated[4] as the explanation for a variety of severe cardiovascular lesions, sometimes causing sudden death. With this advance of our understanding of Marfan's syndrome its status changed accordingly from that of a disfiguring but otherwise innocuous skeletal malformation to one frequently associated with incapacitating anomalies of the eyes and always fraught with the potential danger of progressive and ultimately fatal cardiovascular disorders.

Clinical Features: Following are listed the more common manifestations of Marfan's syndrome:

I. *Skeleton*
  (A) Long, thin extremities and spider fingers[1,5,6]
  (B) Hypoplastic musculature, scant panniculus, and flaccid ligaments[1,5,7]
  (C) Chest deformities (funnel- or pigeon-chest, kyphosis)[4,5,8–10]
  (D) Brittleness of bones[10]

II. *Eyes*
  (A) Congenital ectopia lentis[3,5,11,12]
  (B) Severe myopia, spontaneous retinal detachment[13]

III. *Cardiovascular System*
  (A) Congenital anomalies:
    (1) interatrial septal defects[2,14]
    (2) deformed valvular cusps[14–19]
    (3) aortic coarctation[6,9,15,20,21]
  (B) Medial degeneration of the great vessels causing:
    (1) dilation of the aortic ring or rupture of the aortic cusps producing aortic regurgitation[4,9,22–25]
    (2) fusiform dilatation of the aorta,[18,19,26–29] or of the pulmonary artery,[4,9,16,30–33] or saccular aneurysms, particularly of the sinuses of Valsalva[2,9,25,26,30]
    (3) dissecting aneurysm, acute or chronic, of the aorta,[16,17,20,26,33–38] or the pulmonary artery[16,31]

Clinical Variations: Marfan's syndrome is a hereditary anomaly of dominant Mendelian character. Its manifestations probably stem from a biologic inferiority of certain body elements,[39] mainly of mesenchymal origin.[5] In different individuals who are afflicted with the disorder, the affected structures are involved in different combinations and to different degrees. Occasionally, one member of an afflicted family may exhibit nothing but a strikingly tall and lean habitus, another one ectopia lentis only, while a third may die suddenly from a

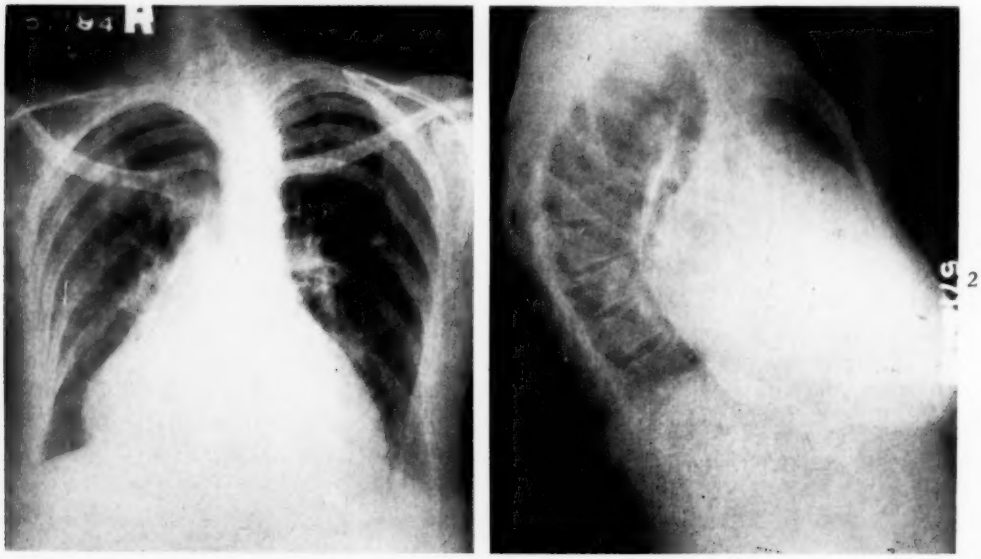

Fig. 1. Chest film shows considerable widening of the cardiac silhouette on both sides. No widening or elongation of the aorta is seen. The thorax is deformed by kyphoscoliosis.

Fig. 2. Lateral view of the chest shows dorsal kyphosis and marked enlargement of the entire cardiac shadow with backward displacement of the esophagus.

Fig. 3. Photograph of the right hand, showing the unusually long and narrow hand and fingers.

Fig. 4. Roentgenogram of the fingers shows the spider-like appearance produced by the abnormal length of the metacarpal bones and phalanges.

dissecting aneurysm during adolescence. Some of the features are evident from early youth, such as the disproportionate length of the extremities and digits, congenital cardiac defects, or ectopia of the ocular lenses. Other manifestations of the syndrome, however, tend to develop gradually and thus are noticed only later in life, such as clouding of the lenses or fragility of the bones. This holds particularly true of most of the important cardiovascular lesions in Marfan's syndrome. Actually, congenital lesions (such as septal defects, valvular deformities, or aortic coarctation) are quite rare in Marfan's syndrome. More commonly, serious cardiovascular disorders do not appear before adolescence or early adult life in individuals previously free of subjective and objective evidence of heart disease.

Anatomic Basis of Syndrome: It appears evident now that in such persons the muscular and elastic elements of the tunica media of the great vessels have been inherently defective since birth.[4,14,18,19] In the course of life focal degeneration develops in the elastic lamina, causing loss of strength and resilience of the vessel wall. The resulting changes resemble grossly those produced by syphilitic aortitis or by Erdheim's cystic medial necrosis, respectively; i.e., either (1) fusiform or saccular aneurysmal dilatation of the root of the aorta (rarely of the pulmonary artery) and stretching of the aortic ring producing aortic regurgitation, or (2) acute (more rarely chronic) dissecting aneurysm of the aorta or pulmonary artery producing rupture of the vessel walls or of the cusps. In contrast, however, to the course of events in syphilitic aortitis and aortic medial necrosis, in Marfan's syndrome these complications develop early in life.

Discussion of the Reported Case

For the reasons listed above, we attributed the cardiac findings in our patient to Marfan's syndrome. Accordingly, the aortic regurgitation was ascribed to dilatation of the aortic ring, and the apical diastolic murmur was interpreted as being probably an Austin Flint phenomenon. The possibility of a mitral valve deformity as a part of the syndrome could not completely be ruled out.[30] The displacement of the esophagus was not thought to be unequivocal evidence of left atrial enlargement, since similar deviation of the esophagus has been reported in cases of Marfan's syndrome in which on necropsy the mitral valves were found normal.[14] In one such case verified at autopsy, the displacement

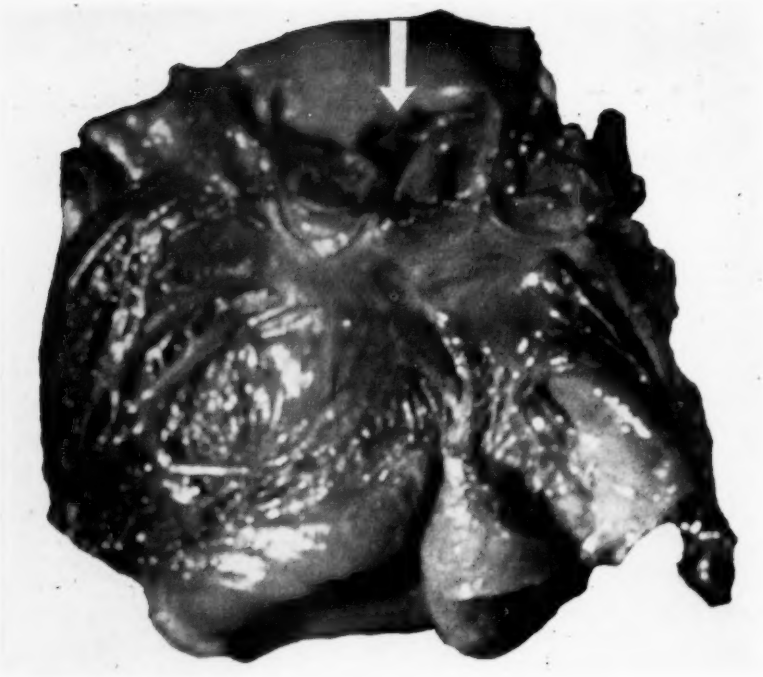

Fig. 5. The heart shows dilatation of the left ventricle. The posterior mitral cusp is redundant and appears ballooned out. The aortic ring is widened. The sinuses of Valsalva show marked aneurysmal dilatation (*arrow*). The bases of the aortic cusps are pulled into the dilated sinuses.

Fig. 6. Section of the supracardiac aorta (low power, elastic tissue stain) shows cystic spaces in the media.

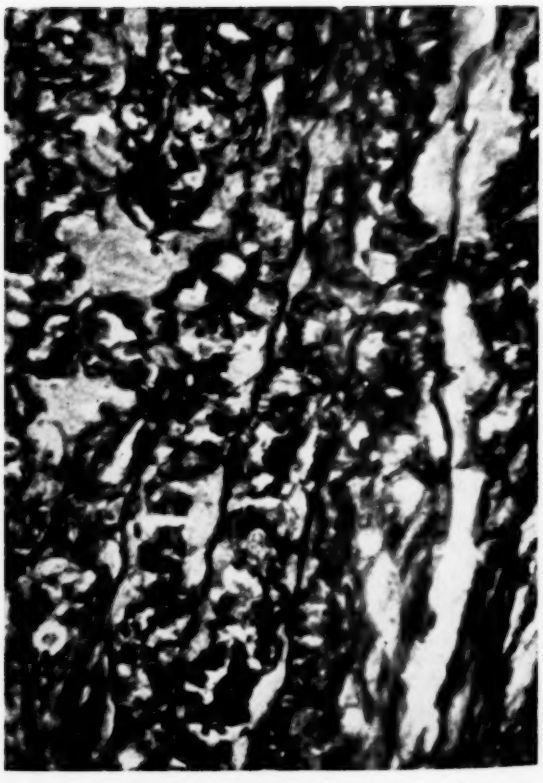

Fig. 7. Section of the supracardiac aorta (high power, elastic tissue stain) shows cystic spaces due to wide separation of the elastic fibers.

of the esophagus was apparently caused by the aneurysmal dilatation of a sinus of Valsalva.[5]* The fact that x-ray examination did not reveal dilatation of the aorta (which we had considered the cause of the aortic regurgitation), did not seem to rule out such a condition, since in Marfan's syndrome the dilatation has often been found limited to the intrapericardial portion of the aorta. In such cases it has involved mainly the sinuses of Valsalva and thus escaped detection by routine radiographic technique.[9,30] Angiocardiographic studies, however, have, in cases of arachnodactyly, repeatedly revealed the clinically unsuspected presence of this type of aneurysm.[40]

Since in Marfan's syndrome congestive heart failure notoriously pursues a rapid downhill course, the prognosis in our patient was considered grave. Actually, her condition improved briefly on digitalis and diuretic treatment. However, three weeks after admission to the hospital she died suddenly without any spectacular terminal symptoms.

Autopsy Report of Heart and Great Vessels

Heart (Fig. 5): The weight of the heart was 650 Gm. The epicardium showed a considerable amount of fat. Both right and left ventricular chambers and atria were markedly dilated. The thickness of the right ventricle was 0.3 cm and that of the left ventricle 1.5 cm. In both auricular appendages small adherent thrombi were found. Elsewhere the endocardium was thin and transparent.

The mitral valve showed redundancy of the posterior cusp, which appeared ballooned out. The cusps were not fused. There were small nodules on the free edge of both cusps of the mitral valve. The chordae of the posterior cusp were slightly thickened but not shortened.

The aortic ring was widened. The cusps were slightly rolled unto their aortic aspects. The commissures were not separated. The aortic cusps, however, did not coaptate because their bases were pulled into the sinuses of Valsalva which had undergone considerable aneurysmal dilatation.

The valve ring circumferences were: tricuspid, 9 cm, mitral 10 cm, aortic 10.5 cm, and pulmonic 9.5 cm. The foramen ovale was patent, the opening was 0.2 cm in diameter. The myocardium showed an area of fibrosis of the interventricular septum. The right coronary ostium was situated unusually high. The coronary arteries were patent throughout their course.

Great Vessels: Above the sinuses, the root of the aorta was dilated for a distance of about 1.5 cm. The distal aorta was of normal size and elasticity. Its intimal surface was fairly smooth with only a rare atheromatous plaque. There was no dissection of the aorta. The major branches of the aorta including the renal arteries were fully patent. The inferior vena cava, iliac veins, and portal vein were unremarkable.

Microscopic Examination: There was hypertrophy of the myocardial fibers and a small area of replacement fibrosis. Sections of the supracardiac aorta (Figs. 6 and 7) showed slight fibrous thickening of the intima. In the media, elastic fibers were absent in numerous small areas, especially in the inner layers. The arrangement of the muscle cells was disordered; the course of some of them was perpendicular to the intimal surface.

The immediate cause of death could not be determined.

Comment

Marfan's syndrome is not a rarity; its recognition, therefore, is of practical clinical importance. Numerous cases have been reported, especially in recent years, since the pathogenesis of the cardiovascular lesions and their significance have become better understood. It is now established not only that 70 per cent of all cases of congenital ectopia lentis occur in patients with Marfan's syndrome, but also that certain cardiovascular lesions previously considered "idiopathic" actually are manifestations of this syndrome. Among these are dissecting aneurysm in the young,[9] aneurysmal dilatation of the pulmonary artery,[14,30,32] spontaneous rupture of the aortic valves, and heart disease in patients with funnel chest.[5,41,42] Recent extensive studies of affected families have revealed the great variations in the picture as appearing in different members of these families.[5,9,19,24,43] Classic, fully developed and easily recognized cases of Marfan's syndrome seem rather uncommon in comparison to the incidence of the *incomplete* picture.

Arachnodactyly should therefore be considered in any patient who exhibits unexplained, rapidly progressive cardiac phenomena, especially in a young individual with findings suggestive of rheumatic or syphilitic heart disease. The family history or the examination of relatives may provide the decisive clue. The importance of a correct diagnosis becomes apparent when it is realized that an apparently healthy individual with nothing more than the habitus of arachnodactyly and/or congenital dislocation of the lenses may at any time

* Case J. M. in McKusick's report.

succumb to rapidly developing cardiovascular complications.[11]

Summary

The case is presented of a 46-year-old Negro woman with the classic features of Marfan's syndrome: spider fingers, ectopia lentis, aneurysms of the sinuses of Valsalva, dilatation of the aortic ring, and aortic regurgitation.

The occurrence of medial degeneration of the great vessels is now recognized to be the most important aspect of the syndrome, since it tends to cause aneurysmal dilatation of the aorta, aortic regurgitation and/or fatal dissecting aneurysm.

These cardiovascular complications may occur in individuals in whom other features of the syndrome are absent or inconspicuous. The presence of more typical anomalies in other members of their family may, however, provide the clue to a correct diagnosis.

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Rupture of an Aneurysm of the Posterior Sinus of Valsalva into the Right Atrium*

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THE recent successful surgical treatment of ruptured aneurysms of the aortic sinuses of Valsalva[1,2] makes the early diagnosis of these uncommon lesions essential. It also becomes important to localize accurately the point of rupture because the surgical attack on those communicating with the right ventricle is more formidable than is the case with rupture into the right atrium. The former is probably best handled by using an extracorporeal pump oxygenator with either induced cardiac stand-still or retrograde coronary perfusion[1,2] while the latter may be repaired utilizing hypothermia and inflow stasis.[2,3] It is often impossible to determine etiology because subacute bacterial endocarditis, one of the most frequent causes of the acquired lesions, may be engrafted on the congenital aneurysms and cause them to rupture.[4–9]

The basic lesion responsible for congenital aneurysms appears to be a lack of continuity between the aortic media and the ring of the aortic valve.[1,5,8,10–12] Occasionally, other associated congenital lesions are seen, including Marfan's syndrome with aortic insufficiency,[13] arachnodactyly,[14] and coarctation of the aorta.[15,16] Complications of aortic sinus aneurysms include aortic insufficiency,[3,10,17] conduction defects,[10,18] angina,[18] myocardial infarction,[19] subacute bacterial endocarditis,[1,9] and rupture. If rupture occurs, immediate and massive congestive heart failure may result.[4,20–22] However, rupture may be insidious—even asymptomatic—and death may not occur for many years.[1,5,20,23] The average life span after rupture is about one year.[1,3,8]

Approximately two-thirds of the congenital lesions arise from the right coronary sinus.[3,24] About 70 per cent of the aneurysms whose origin are in the right sinus rupture into the right ventricle.[3] Less than one-third of congenital aneurysms occur in the posterior (noncoronary) sinus and all 12 recorded cases have ruptured into the right atrium.[3,5,8,9,24–27] The left sinus is rarely involved.[3] At least two cases with aneurysms of two sinuses[10,25] and four patients with lesions involving all three sinuses[11,24] have been reported. Seventy-five per cent of patients who had congenital aortic sinus aneurysms were under 30 years of age at the time of discovery.[1,26] About 75 per cent were male.[8] The youngest patient reported was four years old.[23] The shunting of blood after rupture is from the aorta to the right atrium or ventricle and is readily demonstrated by cardiac catheterization.[1,3–6,23,24,28] Retrograde aortography may delineate the lesion[1,24] even if it has not ruptured. Congenital aneurysms which rupture are remarkably similar in appearance;[1,3,8,27] they are funnel-like, thin-walled, and small, and the point of rupture is at the apex of the aneurysmal sac.

Cyanosis does not occur[12,29] unless shock is present at the time of rupture or later when left-sided failure follows.[28] Chest pain, which is often severe and tearing,[1,22,28] can help time the rupture exactly. Following rupture a characteristic murmur[1,8,12,28] is readily heard. It is loudest in the 3rd and 4th intercostal spaces, which are lower in location than other continuous diastolic-systolic murmurs, and is occasion-

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ally best heard along the right sternal border.[12,21] The latter is pathognomonic.

Venous pressure is usually elevated with prominent venous pulsations in the neck.[21,27] Electrocardiograms often show right ventricular hypertrophy and right axis deviation. There may be extreme systolic hypertension (which may reach 300 mm mercury)[21,25] but diastolic and mean blood pressure are decreased. Uremia occurs occasionally due to emboli from valvular lesions,[9] but is more frequently unexplained.[28] Concurrent jaundice is sometimes seen due to passive congestion of the liver.[29]

Case History

The patient was a 24-year-old white male college student who entered the Veterans Administration Hospital on December 18, 1957, complaining of weakness and palpitations.

His past history revealed that an asymptomatic heart murmur was first documented in August, 1957, during an insurance examination. A presumptive diagnosis was made of a small interventricular septal defect without cardiomegaly. He denied any symptoms of rheumatic fever at any time. Nothing in his infancy suggested congenital heart disease. There were no stigmata of syphilis and several negative serologic tests for syphilis had been obtained while in service (1951–1954). Before the present illness he had been an athlete and had participated in many competitive sports, including track.

Later in August, 1957, he had two dental extractions. A week later his physician treated him with 600,000 units of long-acting intramuscular penicillin and 12 tablets of oral penicillin for fever, cough, and minimal blood streaking of his sputum due to presumed acute bronchitis which had followed the dental work. In the following month the fever disappeared, but facial and brawny ankle edema abruptly appeared. Because of the possibility of a penicillin reaction he was treated with prednisone with temporary remission of edema which immediately returned when the drug was discontinued. His clinical course then rapidly deteriorated and, on December 9, 1957, he was admitted to another hospital because of nausea, fever, chills, cough, hemoptysis, edema, dyspnea, and orthopnea. No pain had occurred.

At that time grade 3 systolic and diastolic murmurs were heard over the aortic area and a remarkable grade 4, harsh, grinding, continuous murmur and thrill were noted in the 4th intercostal space to the left of the sternum. His liver was enlarged and tender, and bounding, dilated neck veins were present. Several palatal petechiae were seen. The spleen tip was palpated by several observers. He was mildly jaundiced and was not cyanotic. Blood pressure was 160/60.

A diagnosis was made of subacute bacterial endocarditis superimposed on a congenital aneurysm of a sinus of Valsalva with rupture into the right ventricle. After five blood cultures were drawn, he was placed on massive antibiotic therapy including intravenous penicillin, 20,000,000 units, oral tetracycline, 2 g, and intramuscular dihydrostreptomycin and streptomycin, 0.5 g each, daily. All five blood cultures were subsequently negative. He was also given digitalis and promptly lost 20 pounds and most of his edema. Nine days later he was transferred to the Veterans Administration Hospital for continued care, further work-up, and possible cardiac surgery. On admission the physical examination was unchanged except for more recent crops of petechiae on the soft palate, conjunctivae, and eyelids. A positive hepatojugular reflux was noted.

Laboratory Findings: Six more negative blood cultures were obtained. Six white blood cell counts and differentials were normal. Hemoglobin gradually fell from 12.9 to 11.2 during his hospitalization. Repeated urinalyses revealed occasional red and white cells and up to 4 plus albuminuria. Blood creatinine rose from 1.2 to 1.4 mg %. Three sputum specimens were negative for tubercle bacilli. Cephalin flocculation was 4 plus. Thymol turbidity: 5.2 units; alkaline phosphatase: 3.1 units; bilirubin: 2.05 mg % (1.35 direct) and 1.67 mg % (1.12 direct). Initially serum proteins were 6 g %; albumin 2.6 g %; globulin 3.4 g %. Repeat proteins were 6.14 g %; albumin 3.74 g %; and globulin 2.4 g %; cholesterol 115 mg %. Serologic test for syphilis was negative.

Electrocardiograms were interpreted as showing combined ventricular hypertrophy. X-ray films of the chest revealed marked generalized cardiomegaly and pulmonary congestion. Cardiac catheterization data, summarized in Table I, showed increased oxygen saturation in the low right atrium and right ventricle.

TABLE I
Catheterization Findings

Site	Pressure (mm Hg)	Oxygen saturation (%)
SVC	18/12	46.5
RA mid	20/12	45.0
low	—	73.5
RV	51/4.1	78.7 (apex)

Hospital Course: For 37 days a gradual downhill course occurred. Daily rectal temperature elevations up to 100.4°F occurred. A slow increase in weight, totaling 6 pounds of edema, was refractory to diuretics. Minor episodes of hemoptysis and epistaxis were frequent. Minimal scleral icterus persisted. Cardiomegaly increased both clinically and by x-ray but active cardiac pulsations were seen at fluoroscopy. His venous pressure remained in the 190 mm range with a positive hepatojugular reflux to 220. The Decholin circulation time was around 35 sec on repeated determinations. More

basilar rales appeared and the edema became more marked. Showers of petechiae continued to appear on the face, arms, and legs.

Because of the increasing severity of his failure the need for surgical intervention became urgent. Cardiac catheterization was performed on the 37th day of his hospitalization in order to obtain data prior to surgery. Toward the conclusion of the catheterization he had severe shaking chills and by the time he was returned to his bed, his rectal temperature was 105.2°F and his pulse was 154. He was cyanotic for the first time and his blood pressure fell to 80/30 from the previously consistent readings of 160/60. The hypotension failed to respond to oxygen, Aramine, and Levophed. Tachycardia and cyanosis persisted. Terminally he had pleuritic right-sided chest pain, and an emergency portable chest x-ray suggested a pulmonary infarct at the right base. Seven hours after cardiac catheterization he died. Cultures of the catheterization equipment and blood were all negative.

Postmortem Findings: At autopsy the globular heart weighed 510 g. All chambers were dilated and flabby. The wall of the right atrium was 4 mm thick. The right ventricle measured 3 mm and the left ventricle 1.4 cm. The commissure of the posterior and right coronary aortic cusps was moderately fused. A saccular aneurysm arose from the posterior sinus of Valsalva and ruptured into the right atrium. It was a thin-walled, diverticulum-like projection, 1.6 cm long and 1 cm in diameter. The 7 mm apical opening was located immediately above the medial cusp of the tricuspid valve (Fig. 1). All of the aortic leaflets were fenestrated[28,30] and slightly thickened (Fig. 2).

No gross or microscopic evidence of subacute bacterial endocarditis or rheumatic heart disease was demonstrated at an abbreviated postmortem examination. No pulmonary infarction had occurred. The lungs were markedly engorged. Many pleural petechiae were present.

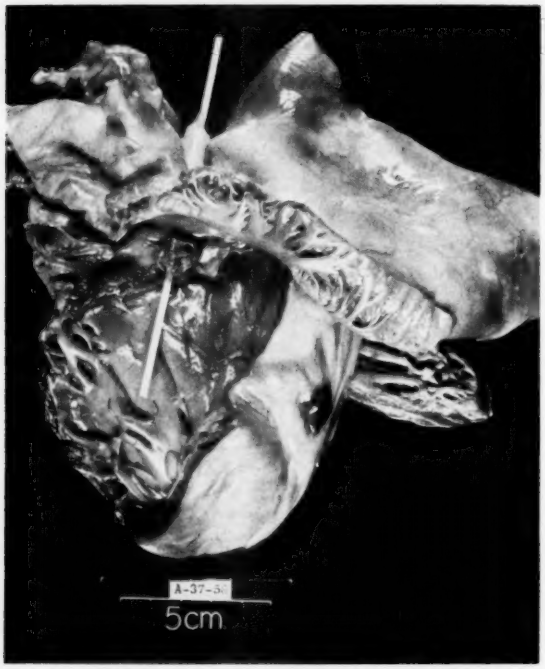

Fig. 1. Probe passes through the intracardiac fistula between posterior sinus of Valsalva and the right atrium. The point of rupture is superior to the median cusp of tricuspid valve.

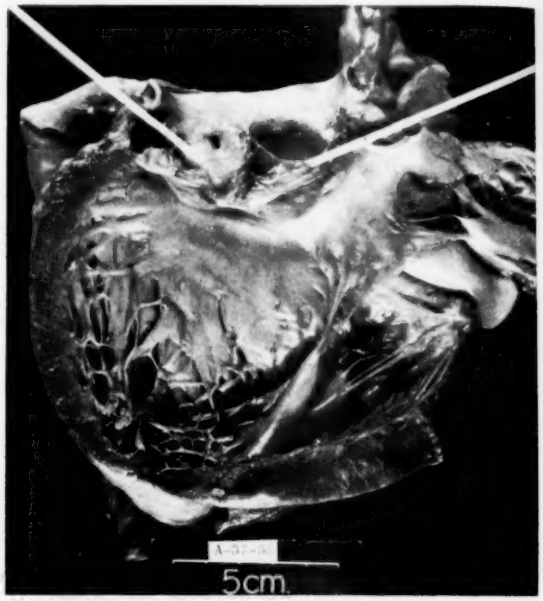

Fig. 2. Fenestrated aortic valve cusps. Right probe lies in the posterior sinus aneurysm.

Discussion

This 24-year-old white male had a congenital aneurysm of the posterior sinus of Valsalva which probably ruptured during an episode of subacute bacterial endocarditis following dental extractions. This infection was altered by the initial penicillin he received before the diagnosis was made and this probably accounted for the negative blood cultures.

The catheterization data revealed differences in the oxygen saturation of the mid and low right atrium; the latter was approximately that of the right ventricle. This strongly suggested that the aneurysm opened into the right atrium rather than the right ventricle. The other possibility was that the arteriovenous fistula entered high in the right ventricle and was associated with tricuspid insufficiency. The location of the apex of the aneurysm and its resultant jet of blood, which was directed into the

outflow tract of the right atrium (Fig. 2), explain the widely divergent oxygen saturation values obtained at different levels in that chamber.

Conclusion

A 24-year-old male died of heart failure following rupture of a congenital aneurysm of the posterior sinus of Valsalva into the right atrium. The rupture apparently occurred during a superimposed subacute bacterial endocarditis which was subsequently healed by intensive antibiotic therapy. Cardiac catheterization showed a marked increase in oxygen saturation in the low right atrium compared to the high right atrial position. This correlated with the autopsy findings of the aneurysm which emptied into the right atrium just above the tricuspid valve. Clinical diagnosis of this lesion was suggested by the characteristic history and physical findings.

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Prolonged Ventricular Asystole in Adams-Stokes Disease

Recovery Following Treatment with the Artificial Cardiac Pacemaker and Massive Doses of Atropine*

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ATTACKS of syncope and convulsions in the Adams-Stokes syndrome pose grave and formidable problems in therapy, chief of which are the unexpectedness and unpredictability of these calamitous episodes. Time is thus of the utmost importance in averting a major catastrophe since the cerebrum cannot be deprived of oxygen for longer than three or four minutes without permanent and irreversible changes taking place. Hence, the importance of quickly determining whether a stated episode of circulatory arrest is due to ventricular standstill or ventricular fibrillation, and to use appropriate and necessary measures without delay. Since circulatory arrest is caused more frequently by ventricular asystole than by ventricular fibrillation,[1] therapy should be predicated upon this assumption unless the latter arrhythmia is known to be operative.

Drugs, cardiac puncture and an externally applied cardiac pacemaker are the only therapy available for atrioventricular block with ventricular asystole. The former two therapeutic modalities, however, are fraught with danger and are often ineffective.

It is important to emphasize the necessity of utilizing the proper terminology in describing episodes of syncope and convulsions associated with atrioventricular block. Zoll[7] has stressed this point and has decried the unfortunate misuse of the terms "Adams-Stokes syndrome" and "Adams-Stokes disease." The Adams-Stokes syndrome consists of two separate entities, namely Adams-Stokes disease and reflex vagal stimulation. Adams-Stokes disease is characterized by permanent atrioventricular block which is present between and during attacks of syncope and seizures. Reflex vagal stimulation, on the other hand, is a transient state which occurs in response to vagal stimulation but which fails to reveal atrioventricular block between the paroxysms of unconsciousness. A classic example of reflex vagal stimulation is the hyperactive carotid sinus syndrome with all its attendant circulatory phenomena. The electrocardiogram is the *sine qua non* in distinguishing both conditions. The distinction between these two conditions is of more than academic interest because differences in clinical course, prognosis and therapy will be determined by the nature of the underlying mechanism involved.

In 1951 Callaghan and Bigelow,[2] and later Herrod and others[3] applied electrodes directly on dogs' hearts rendered asystolic utilizing the open chest technique. They were successful in stimulating ventricular activity by means of a series of monophasic electrical stimuli. The obvious disadvantage of this procedure was the necessity of so desperate a measure as thoracotomy. Zoll[4] advanced a step further in the therapy of cardiac arrest by developing an ingenious apparatus which he used successfully in 2 patients with ventricular asystole for pe-

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riods of 25 minutes and five days, respectively. The latter patient survived and resumed spontaneous ventricular activity. Zoll *et al.*[6,7] demonstrated that this device not only obviated the need for thoracotomy but was also capable of delivering a series of electric stimuli to the external surface of the heart and so functioned as an artificial cardiac pacemaker. The machine initiated impulses to which the ventricles responded until intrinsic ventricular rhythmicity was obtained of a sufficiently effective degree to maintain an adequate circulation. It produced monophasic, rounded electric impulses with an average duration of 2 to 3 milliseconds. In construction this apparatus was lightweight, weighing 13 pounds, was portable and simple to use, obvious advantages which need no further comment. The frequency ranged between 30 to 180 stimuli per minute and the amplitude from 0 to 150 volts. Two circular electrodes 3 cm in diameter are placed on any arbitrary chest position that will give an effective current flow across the heart. In our case, the negative electrode was applied at the point of maximum cardiac impulse and the positive electrode over the right anterolateral chest wall. Electrode paste is used to insure a good electrical contact and a rubber strap encircling the chest holds the electrodes firmly in place.

In 1952 Zoll[4] reported that ventricular standstill with Adams Stokes seizures could be favorably influenced in man by his mechanical cardiac pacemaker. In the intervening two years, Zoll and his co-workers[5,6,11] collected a series of 11 cases of ventricular standstill with the Adams-Stokes syndrome, of which nine were successfully treated with the cardiac stimulator for prolonged intervals varying from 25 minutes to 108 hours. They obtained their best results using an electric current ranging between 75 and 150 milliamperes and a voltage of from 45 to 100 volts. Zoll[5,8] and other investigators[9] found no serious cardiac sequela in their patients from external electric stimulation. Neither multiple ectopic ventricular beats nor ventricular fibrillation were found in the electrocardiogram, in contrast to these same ectopic rhythms which were often seen experimentally in direct electrical stimulation of the exposed heart. For the sake of completeness, it is worthy of note that minor untoward effects of stimulation have occurred, of which superficial skin ulcerations directly beneath the chest electrodes were by far the commonest encountered. Chest pain and an annoying generalized muscular contraction were also common unpleasant side reactions.

Rosenbaum and Hansen[9] in 1954 devised a cardiac stimulator which combined a defibrillator and a pacemaker, incorporating a blocking oscillator circuit without the necessity of opening the chest cavity. They demonstrated the effectiveness of their machine in a patient with complete heart block in whom it was used intermittently over an eight-hour period for a total of two and one-half hours and favorably maintained an adequate cardiac output.

Starzl, Gaertner, and Webb[12] studied the effectiveness of the electrical pacemaker in dogs with experimental cardiac arrest induced by asphyxia, quinidine intravenously and chloroform inhalation. They found that 85 per cent of the animals lost their power of myocardial contraction much sooner than the intrinsic initiation of the electrical impulses. The pacemaker was of no value in treating these animals. In the remaining 15 per cent of the dogs who developed complete heart block with ventricular standstill and who maintained a potentially good myocardial contractility the cardiac pacemaker was of distinct therapeutic benefit.

By 1955 Zoll and his colleagues[6,7] had resuscitated 29 patients with Adams-Stokes attacks with their electric cardiac pacemaker. In 1955 Douglas and Wagner[10] reported a case of ventricular standstill in a 72-year-old man with the Adams-Stokes syndrome who recovered after treatment with the cardiac pacemaker for seven days continuously before spontaneous idioventricular rhythm was restored.

Jackson *et al.*[13] in 1957 reported the use of the cardiac pacemaker intermittently for more than seven months in a patient with Adams-Stokes disease associated with cardiac hypertrophy of unknown etiology. This patient was taught to operate the machine himself and he would turn it on when he felt an impending attack

approaching. He survived for seven months.

We report here a case of Adams-Stokes disease with prolonged ventricular asystole in which the use of the artificial pacemaker was required for five days and led to the patient's recovery.

Case History

A 54-year-old white male entered the Elmhurst General Hospital on January 20, 1958, because of weakness, nausea, vomiting, and numerous intermittent episodes of vertigo and syncope of six hours' duration. These attacks of unconsciousness had occurred for the past eight years, the first such following the strenuous exertion of running, and was of ten minutes' duration. He stated that due to the persistent dizziness and syncope after exertion or on change of position, he consulted a physician, on November 7, 1950, who took an electrocardiogram and found a left bundle branch block (Fig. 1A). The blood pressure was 118/80. Five months later, in March, 1951, he experienced another bout of vertigo and unconsciousness. He sustained a deep laceration over his left eye and was hospitalized for a week. An electrocardiogram was taken and revealed a left bundle branch block not unlike the initial tracing recorded four months earlier.

He attempted to work as a mechanic but abandoned

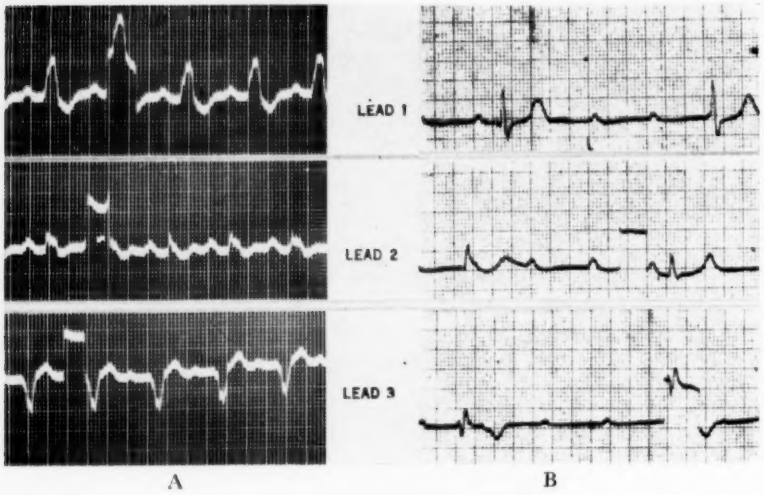

Fig. 1. (A) Electrocardiogram taken on November 7, 1950. Left bundle branch block. (B) Electrocardiogram taken in March, 1951. Complete A-V block; ventricular rate 28.

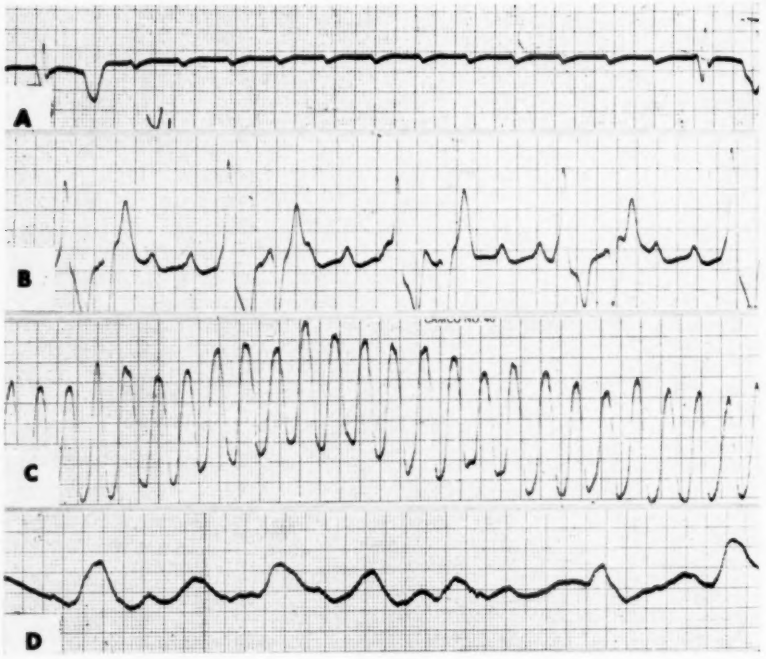

Fig. 2. (A) Initial electrocardiogram (V_1) on admission (Jan. 20, 1958). Complete A-V dissociation; ventricular rate less than 10 per minute. (B) Multifocal ventricular complexes one and a half hours after admission (lead 2). (C) Ventricular tachycardia four hours after admission (lead 2). (D) Ventricular fibrillation (lead 2).

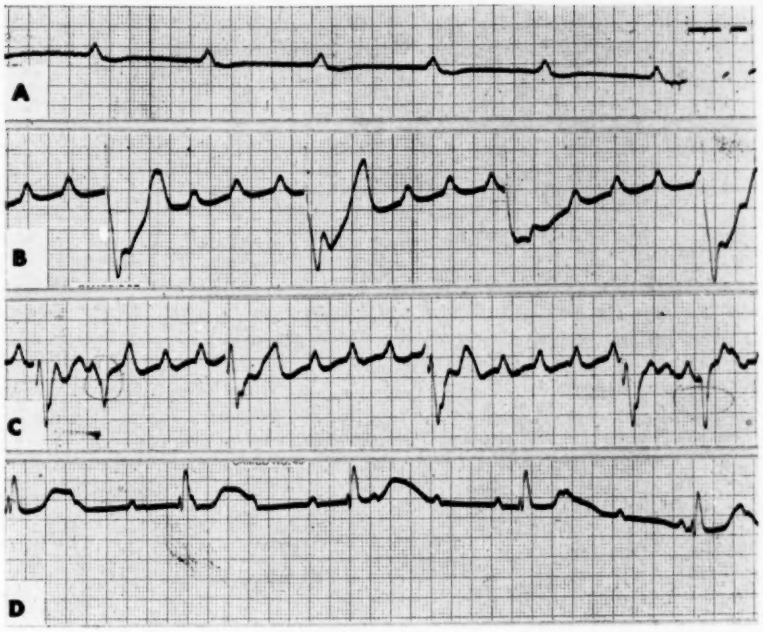

Fig. 3. (A) Jan. 20, 1958. Electrocardiogram five seconds after administration of 100 mg Pronestyl intravenously. Ventricular standstill with some auricular activity still present. Pacemaker started at end of tracing. (B) Jan. 21, 1958. Artificial cardiac pacemaker with ventricular response to the electric stimuli of the pacemaker. (C) Jan. 22, 1958. Spontaneous ventricular impulses fifteen minutes after 2 mg atropine sulfate intravenously. (D) Jan. 25, 1958. Artificial cardiac pacemaker temporarily discontinued. Spontaneous ventricular activity present. (All tracings lead 2.)

it because of frequent dizzy and fainting spells. He noted that the loss of consciousness was of short duration and was associated with a feeling of lightheadedness. He learned to lie down when this feeling occurred and thus prevented further injuries to himself. He took no medication during this entire period.

Between 1952 and 1955 the number of syncopal episodes diminished. Another electrocardiogram taken during this period again showed a left bundle branch block. On January 25, 1955, he was subject to a series of similar seizures and was admitted to the Astoria General Hospital the following day. Here he was informed for the first time that he had a complete heart block with the characteristic Adams-Stokes paroxysms (Fig. 1B). Isuprel 10 mg was administered sublingually six to eight times daily as well as ephedrine in oil 500 mg intramuscularly daily. He was discharged from the hospital on March 13, 1955, with a ventricular rate of 30/min. At this time, the patient noted the onset of syncope when his heart rate was less than 20/min.

In 1956 he was examined by another physician who added ephedrine sulfate orally to his sublingual Isuprel therapy. His syncopal seizures were controlled perceptibly. He did admit, however, that sexual relations precipitated his attacks of unconsciousness.

The patient denied having had rheumatic fever, hypertension, congenital heart disease, diphtheria, or myocardial infarction, or taking the digitalis glycosides orally or parenterally. His familial anamnesis was significant in that one brother developed complete heart block at 28 years of age and died three years later. His father who is 81 years old and still living has had complete heart block for the past four years and has been on 10 mg of Isuprel sublingually three times daily ever since.

CLINICAL COURSE

Six hours prior to his present hospital admission, the patient developed typical Adams-Stokes episodes which were associated with a very slow ventricular rate of between 11 to 16 beats/min. A further drop in the ventricular rate to 4/min precipitated convulsive seizures. The initial physical examination on admission to the hospital revealed a conscious but acutely ill male, pale, weak, and perspiring profusely. His pupils were dilated. The jugular vein was engorged and pulsating. The heart sounds were faint, distant, and irregular with a ventricular rate of 12 beats/min. The blood pressure was 185 systolic and 55 diastolic. There was no peripheral edema. The electrocardiogram on admission showed complete atrioventricular dissociation with a ventricular rate of sixteen impulses per minute (Fig. 2A).

Drug Therapy: The external artificial cardiac pacemaker was attached to the patient but there were no ventricular responses whatsoever to its electric stimuli. The pacemaker apparatus was discontinued and reliance was placed upon the sympathomimetic drugs, Isuprel sublingually and intramuscularly (0.4 mg) and epinephrine 1 ml subcutaneously. One hundred cubic centimeters molar lactate solution were given intravenously. Approximately one hour and a half after entry to the hospital, the electrocardiogram showed multifocal ventricular beats which increased in frequency (Fig. 2B). The patient was conscious but syncopal episodes kept recurring without any associated convulsive paroxysms. It was decided at this point to take continuous electrocardiographic records throughout the patient's course in the hospital in order to keep abreast of any sudden new change in cardiac activity

Four hours after admission, the patient ceased to breathe. Electrocardiographic studies revealed that the multifocal ventricular beats were now replaced by a ventricular tachycardia (Fig. 2C) and, in turn, by ventricular fibrillation (Fig. 2D). It was our opinion that these disturbing ectopic arrhythmias were the result of the large doses of sympathomimetic amines which the patient was receiving. He was now given 100 mg of Pronestyl intravenously and within five seconds the ventricular fibrillation disappeared and was followed by ventricular asystole, though some auricular activity persisted (Fig. 3A). The patient now exhibited apnea, shock and frequent convulsive movements. The artificial cardiac pacemaker was again activated. The apnea persisted for 15 minutes, during which period it was necessary to use artificial respiration in conjunction with oxygen by nasal catheter. The ventricles now responded to the electric stimuli of the cardiac stimulator machine.

On January 21, 1958, 12 hours after admission to the hospital, the patient was still having convulsive seizures. The electrocardiogram showed the same complete absence of spontaneous ventricular activity except for the responsive beats to the electrical stimuli of the artificial pacemaker (Fig. 3B). He was semiconscious and the blood pressure was maintained at 160 systolic and 90 diastolic.

Effect of Atropine: On January 22, 1958, the third hospital day, his condition remained grave and because of his critical state, it was felt that the administration of large doses of atropine sulfate might prove beneficial in neutralizing any reflex vagal effects. Atropine sulfate 2 mg was given slowly intravenously. Within fifteen minutes there appeared three spontaneous ventricular impulses on the electrocardiogram (Fig. 3C). One and a half hours later 48 mg of atropine sulfate dissolved in 200 cc of sterile distilled water was started intravenously at a rate of 50 drops/min. One-half hour later the patient became drowsy and gradually lapsed into unconsciousness. Convulsive seizures followed rapidly and continuously despite all efforts. The atropine was discontinued after 30 mg had been given. Four hours later 0.2 mg Isuprel was given intravenously. The patient remained in a comatose condition for ten hours or the better part of the fourth hospital day. He then began to respond to stimuli though he was unable to speak. The blood pressure was 160/50. Several short-lived attempts were made to discontinue the artificial cardiac pacemaker but the failure of the patient to develop his own spontaneous ventricular rhythm and the onset of convulsions again forced us to abandon this abortive effort as premature.

On January 24, 1958, the fifth hospital day, the patient was alert and conscious. He showed an occasional spontaneous ventricular response.

Recovery Period: On January 25, 1958, the sixth hospital day, the patient showed definite improvement. The cardiac pacemaker was lowered to 45 impulses/min. It was not noted that there was spontaneous ventricular activity. The external electric stimuli from the artificial pacemaker were interrupted for a minute at a time without untoward effects (Fig. 3D). The rate of impulse formation of the cardiac pacemaker was still further reduced to 30/min. Isuprel was continued intravenously.

On January 26, 1958, the seventh hospital day, he was comfortable and had a ventricular rate of 48/min. At 9 a.m. the pacemaker was permanently discontinued, after being in continuous use for five consecutive days (Fig. 4A). The patient's course was smooth and uneventful thereafter. He developed superficial skin ulcerations at the site of the electrode contact. These healed rapidly after gentian violet applications. His systolic blood pressure remained elevated throughout his convalescence and this was attributed to the large amounts of the sympathomimetic amines administered throughout his hospital course. An electrocardiographic tracing taken on March 7, 1958, showed complete atrioventricular block (Fig. 4B). He was discharged from the hospital on March 13, 1958, vastly improved over his admission status.

Comment

This patient presented a difficult problem in therapy, notwithstanding a diagnosis of complete

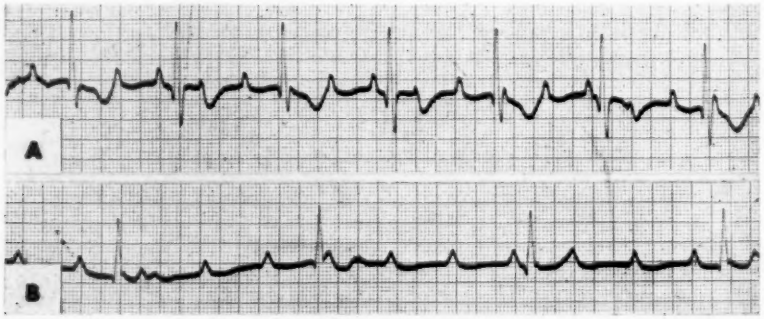

Fig. 4. (A) Jan. 26, 1958. Electrocardiogram after cardiac pacemaker stimulation was permanently suspended. Ventricular rate 55. (B) Electrocardiogram on March 7, 1958 during convalescence. Complete A-V block, ventricular rate 30 (all tracings lead 2).

heart block which was apparent from the very onset. All the classic sympathomimetic drugs were tried with little or no appreciable improvement in the clinical picture. There was no dramatic response to the administration of these pressor amines which included subcutaneous and intravenous epinephrine, intravenous Neo-Synephrine, intramuscular ephedrine sulfate as well as sublingual and intravenous Isuprel. Also used were oxygen therapy, intravenous calcium gluconate and molar lactate solution. The first significant therapeutic effect occurred after the external artificial cardiac pacemaker was applied and electric stimuli to the ventricles initiated. The degree of ventricular response to the pacemaker device was sufficient to maintain a satisfactory cardiac output. The cardiac stimulator tided over a seriously embarrassed heart during a crucial period and substituted an effective extrinsic pacemaker for a faulty functioning "built in" conduction system. The simplicity and easy operability of this apparatus together with minimal side reactions to the patient were factors which made the artificial pacemaker a worthy and welcome addition to the treatment of the heart block.

The time required for resuscitation from Adams-Stokes seizures secondary to ventricular standstill utilizing the artificial cardiac pacemaker is difficult to predict. It depends upon which of the various etiologic factors, alone or in combination, underlies the particular Adams-Stokes attack. At times, no valid explanation can be advanced to explain the sudden explosive onset of Adams-Stokes seizures in a case of asymptomatic atrioventricular block. Among the more common causes of heart block are drug toxicity (digitalis), infectious diseases (diphtheria, rheumatic fever), congenital lesions (often associated with interventricular septal defects), surgical procedures, anesthetics, myocardial infarction, vagal reflexes, neoplasms, and many others. In our case it was necessary to continuously operate the artificial cardiac pacemaker for five days before the intrinsic pacemaker potential was reactivated and the Adams-Stokes attacks were abolished. Other cases reported in the literature have required the uninterrupted use of the artificial cardiac pacemaker for longer or shorter periods, depending upon when the normal intrinsic pacemaker asserted its dominant role again.

This case aptly illustrated the dangerous toxic arrhythmias which may be induced following the use of the sympathomimetic drugs. We attributed the onset of the multifocal ventricular extrasystoles followed rapidly by ventricular tachycardia and ventricular fibrillation to the administration of epinephrine and ephedrine compounds. We did not consider that isopropylnorepinephrine (Isuprel) was a factor in the genesis of the ventricular ectopic arrhythmias because of its unique ability of stimulating the higher centers predominantly, especially the sinus and atrioventricular nodes, and thus accelerating the rate of the pacemaker in heart block. The administration of 100 mg of Pronestyl following the appearance of ventricular fibrillation was a measure born of desperation. We chose to take this calculated risk fully cognizant of the hazard of complete cardiovascular collapse and a fatal outcome.

It is important to emphasize the value of trying large doses of atropine sulfate in heart block with the Adams-Stokes syndrome. We were able to initiate the first spontaneous ventricular contractions following the administration of 2 mg of this belladonna alkaloid. It was not our purpose or desire to infuse the large 30 mg dose of atropine sulfate intravenously as rapidly as was accomplished in our case.

There is a good possibility that the toxic manifestations of atropine (unconciousness and convulsions) could have been minimized with a much slower administration. We believe that atropine sulfate has been unwittingly relegated to a secondary position in atrioventricular block following the introduction of newer therapeutic procedures.

The explanation for the systolic hypertension which our patient exhibited resides in the fact that large quantities of the pressor amines were taken both orally and parenterally. We felt that the hypertension was not of etiologic significance in this case.

The feasibility of using the external artificial pacemaker continuously over a protracted period has been shown to be not only a life-saving measure but also devoid of danger or

serious sequelae. Our patient did develop superficial skin ulcerations at the sites of electrode contact of the chest wall. The use of gentian violet topically was sufficient to heal these excoriations within a week.

It is of interest to note the family history of complete heart block in a brother and in the father of this patient. The presence of familial congenital atrioventricular heart block as a clinical entity has been reported in the literature.[14]

Summary

(1) A case is presented of Adams-Stokes disease with ventricular standstill treated with the external artificial cardiac pacemaker for five consecutive days continuously with complete recovery.

(2) The hazard of producing serious ventricular ectopic rhythms with the sympathomimetic drugs in complete heart block is discussed.

(3) Atropine appeared to trigger the onset of spontaneous ventricular activity.

(4) No serious cardiac sequelae resulted from the use of the artificial cardiac pacemaker. Minor reactions consisting of superficial skin ulcerations beneath the chest electrodes and a generalized muscular contraction were encountered.

(5) Reference is made to the presence of complete heart block in a brother and father of this patient.

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Progress Notes in Cardiology

Edited by EMANUEL GOLDBERGER, M.D., F.A.C.C.

New York, New York

Coarctation of the Aorta and Pregnancy

PREGNANCY is not rare in patients with coarctation of the aorta. Therefore, the possibility of the existence of this abnormality should be considered in every case of hypertension during pregnancy, or soon thereafter. The absence of toxemia of pregnancy and fetal mortality in patients with coarctation of the aorta is impressive, and only one report has been found that mentioned such an occurrence. This is in sharp contrast to the incidence of toxemia of pregnancy in patients with hypertension from other causes, which varies in reports in the literature from 10 to 30 per cent.

Coarctation of the aorta associated with pregnancy is an important abnormality which requires operation in many cases. There is not sufficient evidence to draw definite conclusions about the optimal time for resection. Recently, Drs. W. Raymond Shanahan, Seymour L. Romney, and James H. Currens studied 10 cases of coarctation of the aorta with 24 pregnancies (*J.A.M.A.* 167: 275, 1958). On the basis of their experience, they believe that operation should probably be deferred until after delivery. Because of the apparent lack of cardiovascular complications during labor cesarean section is not necessary, and pelvic delivery can be used for patients with coarctation of the aorta.

Treatment of Fat Embolism with Heparin

IN 1943, HAHN (*Science* 98: 19, 1943) observed that in vivo heparin could "clear" lipemic plasma, rendering it translucent when it had become opalescent after a fatty meal. French, Robinson, and Florey (*Quart. J. Exper. Physiol.* 38: 101, 1953) suggested that fat globules present in the blood of patients suffering from fat embolism might be similarly lysed, reducing the risk of infarction.

Recently, Sage and Tudor (*Brit. M. J.* 1: 1160, 1958) described three patients with fat embolism whom they successfully treated with heparin. These patients included (1) a male, aged 23, with a closed fracture of the right femur; (2) a male, aged 40, with a comminuted closed fracture of the left femur and open fracture of the left tibia and fibula; (3) a male, aged 19, with open fracture of the right tibia. In no case was there any evidence of head or chest injury. The diagnosis of fat embolism was made on clinical signs supported by chest x-rays and sputum examination. Treatment consisted of 25,000 units of heparin daily in two doses given intramuscularly for three days.

Despite the view of de Takats* that there may be regression of symptoms to complete recovery, no matter how serious the initial symptoms, these three cases were of such severity that they might reasonably have been expected to be fatal. Improvement after treatment occurred over 3–4 days, a strikingly short period. Complications noted were hemorrhage at the fracture site in one case and somewhat delayed union and possibly more than usual joint stiffness at the fracture sites in another, this latter

* In CHRISTOPHER, F. (Ed.): *Textbook of Surgery*, ed. 4. W. B. Saunders Company, Philadelphia, 1945, p. 248

being probably due to unavoidable lack of physiotherapy in the early days after injury.

Comments: The diagnoses of fat embolism were made on clinical grounds but were considered to be indisputable. The dosages of heparin were those used in calf-vein thrombosis, and the shortness of the course is noteworthy. It is emphasized that this is only a preliminary trial of heparin in fat embolism, but the result is felt to indicate the value of more widespread trials.

Since the time these patients were treated, however, Gardner and Harrison (*J. Bone & Joint Surg.* 39B: 538, 1957) reported that heparin had little influence on the course of artificially induced fat embolism in rats and that it was not worth a clinical trial in human cases. They found that in animals heparin accelerated death and increased the number of deaths after artificially produced fat embolism.

More recently, Cohen and Sparling (*Brit. M. J.* 1: 1353, 1958) reported successful treatment in two further cases, using a dosage of 2,000 units intravenously every four hours. They stated that "an increase in the dose of heparin results in an increased production of clearing factor until there is a maximum response, after which any increase in the dose of heparin is valueless with respect to the production of clearing factor." A dose of 2,000 units was chosen in spite of the fact that 400 units produced measurable amounts of clearing factor. In their two cases, however, no hemorrhage at the fracture sites was encountered.

The Query Corner

READERS are invited to submit queries on all aspects of cardiovascular diseases. Insofar as possible these will be answered in this column by competent authorities. The replies will not necessarily represent the opinions of the American College of Cardiology, the JOURNAL or any medical organization or group, unless stated. Anonymous communications and queries on postcards will not be answered. Every letter must contain the writer's name and address, but these will not be published.

Postcommissurotomy Syndrome

Query: Have you ever observed a case of "postcommissurotomy syndrome" which lasted for $1^1/_2$ to 2 years intermittently following surgery? The symptoms recur whenever steroid therapy is stopped.

Answer: In our four-year study of patients with "postcommissurotomy syndrome," there were several patients who had recurring attacks for as long as 21 months postoperatively. About half of the patients did not have attacks beyond 4 months. In the others the duration varied from 5 months to 21 months.

We also observed that steroid therapy had no advantage over aspirin, codein, etc., in the treatment of this syndrome and, furthermore, is notorious for its rebound phenomena after cessation of therapy.

WILLIAM LIKOFF, M.D.
Philadelphia, Pa.

Steroid Therapy for Heart Block

Query: What is the present status of steroid therapy for heart block with Stokes-Adams attacks? Should it be tried in every case?

Answer: The status of steroids in the treatment of complete heart block has not been adequately determined at this time. We have successfully used ACTH in the treatment of life-endangering Stokes-Adams attacks following an acute posterior myocardial infarction. Adrenal steroids were also used successfully in three of four patients with chronic complete heart block and Stokes-Adams attacks. Since reporting these results, we have learned by personal communication from doctors of six cases of chronic Stokes-Adams attacks treated with adrenal steroids with reversion to normal sinus rhythm. The etiology in all of these cases was arteriosclerotic heart disease. There is a report in the literature of adrenal steroids being successfully used in complete heart block due to rheumatic heart disease.

It is not known which adrenal steroid preparation is the drug of choice. Our original thought was that the steroid reduced the amount of inflammatory reaction about the conduction system. However, this does not explain the action in chronic cases. Others have shown that adrenal steroids affect the rate of A-V conduction in the intact conduction system as measured by the PR interval. If this effect is mediated through electrolyte changes, then it may well be that certain steroid preparations might be more effective than others.

In light of the above observations it would seem wise to use the steroids in any case of complete heart block if no contraindication exists. It appears to be one of the few methods which is directed at correcting the underlying condition rather than just speeding up the ventricular rate. In the latter instance there is the danger of serious ventricular arrhythmias. It is our belief that adrenal steroids will find a permanent role in the treatment of complete heart block and Stokes-Adams attack.

REXFORD KENNAMER, M.D.
and MYRON PRINZMETAL, M.D.
Los Angeles, Calif.

Left Bundle Branch Block

Query: A 60-year-old male patient was hospitalized for anginal pain for a month. Four tracings taken a week apart showed a left bundle branch block. On the day of discharge a tracing was taken and there was no evidence of any prolongation of the QRS interval in any lead. The patient was kept another day and the tracing again showed widening of the QRS interval. How often does left bundle branch block revert to normal conduction, and can you state something about the mechanism?

Answer: Left bundle branch block that

reverts to normal or nearly normal conduction is not rare. Occasionally this occurs in the absence of any other sign of heart disease. The left bundle branch may become involved in various degrees in any disease that affects the myocardium. Accordingly, its conductivity may be altered in varying degrees.

In angina, myocardial infarction, and other forms of heart disease, left bundle branch block may come and go. When this occurs the conductivity of the bundle is depressed, not abolished. The bundle can conduct when the cycle length is sufficiently long to allow the increased time necessary for the bundle to recover; i.e., its refractory period is simply lengthened above the normal duration. Thus, bundle branch block may appear when the rate is increased (often slightly) and disappear when the rate is diminished. If the increase in the duration of the refractory period is small the rate may have to become quite rapid before left bundle branch block appears. With extremely rapid rates even the normal left bundle branch may fail to conduct. (However, QRS aberrations in supraventricular tachycardia are usually of the right bundle branch block type.) If the increase in the duration of the refractory period is greater, left bundle branch block may be present at ordinary rates but will disappear for one or more beats after a long pause resulting from a ventricular premature beat or from carotid sinus stimulation.

Once bundle branch block is abolished by slowing of the heart rate it may remain absent after the heart rate has again increased to a rate at which block was originally present. One possible explanation for this has been suggested (GARDBERG, M.: *Am. Heart J.* 55: 677, 1958). This may explain why it is that when short strips of records are compared the presence or absence of left bundle branch block does not seem to depend upon rate. On the other hand, the processes which depress conductivity (ischemia in angina, inflammatory edema in infarction, excessive dosage of quinidine) vary quantitatively, as they must in this case; this and probably other factors (electrolytes) are undoubtedly involved.

MANUEL GARDBERG, M.D.
New Orleans, La.

Book Reviews

The Chemical Prevention of Cardiac Necroses, by Hans Selye. The Ronald Press Company, New York, 1958, pp. 235, $7.50.

In the preface to his latest book, the author says: "Observations on cardiac necroses are now scattered throughout the world literature. The object of this monograph will be to coordinate these data in the light of newly acquired knowledge about the electrolyte-steroid cardiopathies." In fulfilling this purpose, Selye has given another shining example of his remarkable, nearly visionary ability to build meaningful systems of thought from seemingly incoherent, separate observations of others, bringing to fruitful life a multitude of individually sterile clinical and experimental facts that had been buried in the vast cemeteries of literature. But even far beyond this bold "horizontal" approach to the problem of the myocardial necroses, the author and his co-workers have contributed a stupendous mass of strategically organized original research (on more than 30,000 rats in less than a year!) to consolidate the thesis that cardiac necroses (chiefly subendocardial) develop under the influence of certain electrolytes (especially sodium phosphates and sulfates), provided that the heart muscle has been "conditioned" to their injurious effects by certain glucocorticoids (especially 2α-methyl-9α-chlorocortisol) or by dihydrotachysterol; furthermore, that various stressful conditions (heat, cold, strenuous exercise, trauma, vagotomy, etc.) provoke the formation of necroses in corticoid-conditioned hearts, even without electrolyte additions; and, finally, that KCl and $MgCl_2$ (by virtue of both their cations and anions) exert a potent protective action against all necrosis-producing factors.

Extensive tabulations demonstrate the step-by-step progression of the experimental plan to either establish or rule out large numbers of electrolyte compounds, steroids, and other agents and conditions as participating or not participating in the causation or prevention, respectively, of the necrotizing processes.

Whether or not application of KCl and $MgCl_2$ will prove clinically useful in favorably influencing "Fiedler's myocarditis," infectious lesions of the myocardium, and other cardiac necroses remains to be seen. Whatever the immediate practical value of Selye's findings may be, if any, his work is to be welcomed as a vigorous and convincing aid to those who are struggling against the traditional obsession of clinical cardiology with the time-honored and convenient but untenable idea that only mechanical interferences with coronary blood flow (atheromatosis, mythical "spasms") can give rise to degenerative changes of the myocardium. The emphasis on the importance of electrolytes in conjunction with conditioning corticoid action in affecting myocardial cell structure is excellently supported and constitutes the core of the book.

In his summary, Selye mentions two "severe flaws" in his concept, namely (a) that certain "stressors" (e.g., spinal cord transsection at C7) failed to elicit cardiac necroses and (b) that "the postulated common metabolic derangement in the cardiac muscle fiber that we believe is induced by stress under certain conditions has not been identified."

As far as these two points are concerned, it seems somewhat surprising, yet in agreement with the author's familiar interpretation of the "stress syndrome," that he persistently underestimates or even completely disregards the fundamental role of the neurovegetative system and of the potential cardiac toxicity of its neurohormones epinephrine and norepinephrine in the mechanism of general stress reactions as well as in the origin of stress-induced cardiac injury. Epinephrine and norepinephrine are not merely injectable drugs but biological agents, at all times present in the heart muscle, discharged in excess under the very stresses experimentally applied by Selye (but not after severance of the cervical spinal cord; see above), overwhelmingly active after vagotomy, causing chemical myocardial hypoxia (despite coronary dilatation) and potassium depletion of the myocardium, typically producing subendocardial necroses, and indirectly stimulating the discharge of glucocorticoids from the adrenals. Thus, the adrenosympathogenic catecholamines appear

as the logical common denominator, the "missing link." A very large body of international literature concerning the physiologic and pathogenic effects of the catecholamines has accumulated since Cannon's studies of the "emergency reaction" of the adrenal medulla under stress and the discharge of "sympathin" from the adrenergic nerve terminals. Its incorporation into the stress concept is overdue and deserves to be seriously considered.

This criticism is not in any way intended to detract from the merits of Selye's monumental new contribution but rather to facilitate the filling of a conspicuous gap in his reasoning. He himself deplores the nearly unavoidable unfamiliarity of many investigators with existing work in related fields. As far as the problems in question are concerned, it should not be too difficult to overcome this handicap.

W. RAAB, M.D.

Heart Disease in Infancy and Childhood, by John D. Keith, Richard D. Rowe, and Peter Vlad. The Macmillan Company, New York, 1958, pp. 877, $22.50.

This book is a timely publication reflecting the rapid increase in interest and achievement in the field of pediatric cardiology. Maude Abbott pioneered in collecting and correlating the pathology of congenital cardiac anomalies. Helen Taussig subsequently focused attention upon the clinical recognition of these conditions and has stimulated an entire school of investigators in this field. Recent books by Kjellberg *et al.* from Stockholm and Nadas from Boston were based entirely upon the authors' observations of their experiences at two centers engaged in the investigation and management of children with congenital malformations of the heart. These books were not intended to be works of reference. The present publication has the broader aim of covering the entire field of heart disease in children, congenital and acquired, and is intended as a work of reference as well as a report of the authors' personal observation in this field.

Following a short introductory chapter on the incidence of congenital and acquired heart disease in childhood, six chapters are devoted to a discussion of diagnostic tests. Subjects covered include electrocardiography, oximetry, cardiac catheterization, and angiocardiography, as well as discussions of heart sounds, murmurs, and pressure determinations. The chapters on cardiac catheterization and angiocardiography should be extremely useful, particularly to the cardiologist or internist who does not see large numbers of children. They reflect the observations and critical opinion of an experienced team with a wide experience. A discussion of the embryology of cardiac malformations and a very brief chapter on familial occurrence precedes discussions of the individual types of malformations and diseases of the heart.

The section of the book dealing with congenital defects represents a detailed report of the authors' wide experience in this field as well as a review of the literature. No attempt is made to review all articles; however, adequate references are tabulated. A tremendous amount of valuable data is well illustrated and very well organized. At times, as in the discussion of endocardial fibroelastosis, a very personal point of view is expressed which does not reflect the opinion of most observers. The acquired diseases of the heart are well covered, the space allotted to a particular disease being proportional to the incidence of that disease in childhood. The discussion of rheumatic fever and rheumatic heart disease is far more comprehensive than that of rheumatoid arthritis or the collagen diseases. The short chapters covering the cardiac manifestations of diseases of the kidney, the thyroid gland, and other organ systems add little to what is available in other texts covering this subject. However, the references following each chapter will be found most useful to those wishing to explore the literature of any specific subject more thoroughly. A compilation of drugs and dosages for infants and children with heart disease will be found to be extremely useful.

This book is the result of years of clinical observation and research in a field which is coming of age most rapidly. It should prove to be indispensable to cardiologists, internists, and general practitioners interested in the management of children with heart disease.

SIDNEY BLUMENTHAL, M.D.

Electrocardiogram Clinics, by Joseph E. F. Riseman and Elliot L. Sagall. The Macmillan Company, New York, 1958, pp. 259, $10.50.

This book is essentially a description of a variety of cases in which the electrocardiogram is employed as a diagnostic method. It also contains a number of general discussions.

The discussion of the treatment of angina pec-

toris is excellent, reflecting a wholesome attitude toward the management of the patient's activity. Another excellent exposition is "Clinical Pictures Which Should Suggest the Possibility of Myocardial Infarction." The discussion of the limitations of electrocardiography in the diagnosis of coronary disease is good. There are many excellent presentations of individual cases and their electrocardiograms.

On the basis of his own experience the reviewer must offer objections to the repeated statement that pain in the chest in angina must be in the anterior chest, for he has seen many cases in which it is located in the posterior chest only. Objection must also be offered to the lack of emphasis upon the importance of the emotional precipitation of attacks of angina, which is so very common, and to the overemphasis of "the shortness of duration of the attacks." In general the description of the distribution of the discomfort in angina is inadequate and may be misleading.

The greatest exception must be taken to the table "Normal Variations of S-T Segments and T waves," on page 15. It indicates that negative T waves in leads 2, V_4, V_5, and V_6, are always abnormal, which is not true (especially when the rate is rapid), and that RS-T segment depressions in all leads are abnormal if they exceed a magnitude of 0.5 mm, which also is not true. Such a table also tends to diminish the importance of shifts that are smaller than 0.5 mm and which yet may be abnormal. Disagreement with the authors here accounts for disagreement with the discussion of several of the cases, particularly those in which the electrocardiogram is interpreted as abnormal because the T waves are low, or RS-T segments are deviated. Many of the errors of interpretation that might be involved in the use of the above-mentioned table are avoided by the commendable repeated emphasis upon serial observation.

MANUEL GARDBERG, M.D.

Normale und pathologische Entwicklung des menschlichen Herzens, by Kl. Goerttler. Georg Thieme Verlag, Stuttgart, 1958, pp. 123, $7.85.

The world-wide effort toward greater understanding and increased knowledge of congenital heart disease would be well served by a lucid description of the normal and abnormal embryology of the heart. The international literature is remarkably devoid of it. The embryologist with the numerous fundamental controversies facing him will feel obliged to throw his weight and opinion pagewise from Spitzer to Pernkopf to Hertwig or disagree with them in part or altogether.

Goerttler's book is not intended to be a complete text on cardiac embryology but rather a platform to present the author's "dynamic" theory of genesis of congenital cardiac defects. The general discussion of the disputes—Spitzer's, Pernkopf's and the author's own—are clearly presented in diagrams and discussed against an extensive perusal of the literature. The author advocates replacing the phylogenetic and anatomic theories of Spitzer and Pernkopf with his own "dynamic" etiologic concepts. Twenty-one selected cases are used to supplement the theoretical discussions.

The text is well written and illustrated, the discussion clearly presented. Illustrations and text are superbly printed. Being addressed to the embryologist and cardiac pathologist, it points out most clearly the need for a book on the normal and abnormal embryology of the heart that is useful to the cardiologist and cardiac surgeon.

ARTHUR GRISHMAN, M.D.

RECEIVED FOR REVIEW

All books received will be acknowledged in this column. Insofar as possible, as space permits, books of special interest will receive more extensive reviews.

A Practice of Thoracic Surgery, by A. L. d'Abreu. Edward Arnold Ltd., London, 1958 (Williams & Wilkins Company, Baltimore, exclusive American agents), pp. 619, $19.00.

The Year Book of Medicine (1958–59 Year Book Series), edited by Paul B. Beeson *et al.* Year Book Publishers, Inc., Chicago, 1958, pp. 782, $7.50.

Cardiovascular Diseases, ed. 3, by David Scherf and Linn J. Boyd. Grune & Stratton, Inc., New York, 1958, pp. 829, $17.75.

Reminiscences and Adventures in Circulation Research, by Carl J. Wiggers. Grune & Stratton, Inc., New York, 1958, pp. 404, $9.75.

The Pathology and Management of Portal Hypertension, by R. Milnes Walker. Edward Arnold Ltd., London, 1959 (Williams & Wilkins Company, Baltimore, exclusive American agents), pp. 113, $8.00.

Current Therapy–1959: Latest Approved Methods of Treatment for the Practicing Physician, edited by Howard F. Conn. W. B. Saunders Company, Philadelphia, 1959, pp. 781, $12.00.

Intra Vascular Catheterization, edited by Henry A. Zimmerman. Charles C Thomas, Publisher, Springfield. Ill., pp. 782, $16.75.

College News

AMERICAN COLLEGE OF CARDIOLOGY

Eighth Annual Meeting

May 25–29, 1959 Benjamin Franklin Hotel, Philadelphia, Pennsylvania

Scientific Program

First Scientific Session

Tuesday, May 26, 9:00 a.m.–12:30 p.m.

Symposium on

SOME CARDIOVASCULAR ASPECTS OF SPACE MEDICINE

Moderator: ASHTON GRAYBIEL, F.A.C.C., CAPT., MC, USN, Pensacola, Fla.
Director of Research, U.S. Naval School of Aviation Medicine

1. Equipment and Techniques for Studying Cardiovascular Problems in Space.
   NORMAN LEE BARR, CAPT., MC, USN
2. Some Observations on Heart Rate and Cardiodynamics During Weightlessness.
   SIEGFRIED J. GERATHEWOHL, M.D.
3. Animal Experiments in Simulated Space Flights.
   ROBERT T. CLARK, M.D.
4. Fat Metabolism and Space Travel.
   G. DOUGLAS TALBOTT, M.D.
5. A New Method of Protection Against the Effects of Acceleration on the Cardiovascular System.
   M. G. WEBB, LT. CDR., MC, USN
   Motion picture on weightlessness.

11:00–11:30 a.m.—Intermission

PRESENTATION OF SCIENTIFIC PAPERS

Chairman: LOUIS F. BISHOP, M.D., F.A.C.C., New York
Assistant Clinical Professor of Medicine, New York University Medical School

1. The Electrocardiogram During Physical Exercise.
   ALVIN H. FREIMAN, M.D., PAUL RUEGSEGGER, M.D., RAMON ABARQUEZ, M.D., and JOHN S. LADUE, M.D., F.A.C.C., New York
   Department of Medicine, Memorial Center for Cancer and Allied Diseases and Sloan-Kettering Institute
2. Serum Triglyceride and Radioactive Fat Tolerance Studies in Coronary Artery Disease.
   DONALD BERKOWITZ, M.D., JOHN J. SPITZER, M.D., and WILLIAM LIKOFF, M.D., F.A.C.C., Philadelphia
   Departments of Medicine, Physiology, and Radiology, Albert Einstein Medical Center, Northern Division, and the Hahnemann Medical College
3. Thromboendarterectomy for Coronary Artery Disease.
   CHARLES P. BAILEY, M.D., F.A.C.C., DRYDEN P. MORSE, M.D., and WILLIAM M. LEMMON, M.D., Philadelphia
   Department of Surgery, Bailey Thoracic Clinic, Hahnemann Medical College

Second Scientific Session

Tuesday, May 26, 1959, 1:30–5:30 p.m.

Symposium on

BIOPATHOPHYSIOLOGY OF ARTERIOSCLEROSIS

Moderator: E. GREY DIMOND, M.D., F.A.C.C., Kansas City, Kan.
Professor and Chairman, Department of Medicine, and Director of Cardiovascular Laboratory, University of Kansas Medical Center

1. Pathogenesis.
   AARON KELLNER, M.D., New York
   Director of Central Laboratories and Associate Professor of Pathology, New York Hospital-Cornell Medical Center

2. Fat Transport and Metabolism.
   DONALD S. FREDRICKSON, M.D., Bethesda
   Investigator, Section on Metabolism, National Heart Institute, Bethesda, Md.

3. Coagulation and Fibrinolysis.
   TAGE ASTRUP, M.D., Copenhagen
   Carlsbergfondets Biologiske Institut

2:45–3:15 p.m.—Intermission

4. Genetics and Epidemiology.
   ANCEL KEYS, M.D., Minneapolis
   Professor of Physiology and Director, Laboratory of Physiological Hygiene, University of Minnesota School of Medicine

5. Hormonal Factors.
   HOWARD A. EDER, M.D., New York
   Associate Professor of Medicine, Albert Einstein College of Medicine

6. Other Aspects of Treatment.
   DAVID ADLERSBERG, M.D., New York
   Associate Attending Physician for Metabolic Diseases, Mt. Sinai Hospital; Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

Fireside Conferences

Tuesday, May 26, 8:30–10:30 p.m.

1. Postmyocardial Infarction Syndrome and Postpericardiectomy Syndrome.
   WILLIAM LIKOFF, M.D., F.A.C.C.,* Philadelphia, and WILLIAM DRESSLER, M.D.,† New York
   *Associate Professor of Medicine, Director, Cardiovascular Section, Hahnemann Medical College and Hospital, Cardiologist, Bailey Thoracic Clinic

2. Effect of Heart Disease on Pulmonary Function.
   GEORGE R. MENEELY, M.D., F.A.C.C.,* and DANIEL S. LUKAS, M.D.†
   * Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.; † Associate Professor of Medicine, Cornell University Medical College, New York

3. Myocardial Metabolism.
   RICHARD J. BING, M.D., F.A.C.C.,* and RICHARD GORLIN, M.D.†
   * Professor of Medicine, Washington University School of Medicine, St. Louis; † Associate in Medicine, Peter Bent Brigham Hospital and Harvard Medical School, and Director of the Cardiovascular Laboratory, Boston

4. Fibrinolysis in Arteriosclerosis.
   TAGE ASTRUP, M.D.,* and EUGENE E. CLIFFTON, M.D.†
   * Carlsbergfondets Biologiske Institut, Copenhagen; † Associate Professor of Clinical Surgery, Cornell University Medical College, New York

5. Indications and End Results for Surgery of Aortic Disease.
   ROBERT P. GLOVER, M.D., F.A.C.C.,* and DWIGHT E. HARKEN, M.D., F.A.C.C.†
   * Director, Thoracic and Cardiovascular Surgery and Research, Presbyterian Hospital, Assistant Professor of Clinical Surgery, University of Pennsylvania, School of Medicine, Philadelphia; † Associate Clinical Professor at Harvard and Chief of Thoracic Surgery at the Peter Bent Brigham Hospital, Mount Auburn and Malden Hospitals, Boston

6. Electrolyte Balance in Congestive Failure.
   E. HUGH LUCKEY, M.D.,* and HADLEY L. CONN, M.D.†
   * Physician-in-Chief, New York Hospital, Professor and Chairman, Department of Medicine, Cornell University Medical College, New York; † Assistant Professor of Medicine, University of Pennsylvania, School of Medicine, Philadelphia

7. Subendocardial Infarction.
   MYRON PRINZMETAL, M.D., F.A.C.C.,* and SIMON DACK, M.D., F.A.C.C.†
   * Associate Clinical Professor of Medicine, University of California School of Medicine, Los Angeles; † Assistant Clinical Professor of Medicine, New York Medical College

8. Chlorothiazide and Analogues.
   JOHN H. MOYER, M.D., F.A.C.C.,* and J. RODERICK KITCHELL, M.D., F.A.C.C.†
   * Professor of Medicine, Head of Department of Medicine, Hahnemann Medical College; † Presbyterian Hospital, Philadelphia

9. Surgery of Coronary Heart Disease.
   DAVID S. LEIGHNINGER, M.D., F.A.C.C.,* and CHARLES P. BAILEY, M.D., F.A.C.C.†
   * Director, Cardiac Surgery Research Laboratory of Claude S. Beck, Western Reserve University School of Medicine, Cleveland; † Director, Bailey Thoracic Clinic, Former Professor and

Head, Department of Thoracic Surgery, Hahnemann Medical College and Hospital, Philadelphia

Third Scientific Session

Wednesday, May 27, 9:00 a.m.–12:15 p.m.

PRESENTATION OF SCIENTIFIC PAPERS

Chairman: OSLER A. ABBOTT, M.D., F.A.C.C., Atlanta, Ga.
Associate Professor and Chief, Division Thoracic and Cardiovascular Surgery, Emory University School of Medicine

1. The Relationship Between Electrical and Mechanical Activation of the Heart.
   PHILIP SAMET, M.D., F.A.C.C., ROBERT S. LITWAK, M.D., and WILLIAM H. BERNSTEIN, M.D., Miami, Fla.
   Cardio-Pulmonary Laboratory and the Department of Medicine, Mt. Sinai Hospital, Miami Beach, Florida, and the Division of Cardiology, Department of Medicine and the Department of Surgery, University of Miami School of Medicine, Coral Gables, Florida, and Jackson Memorial Hospital

2. A Simple Method of Recording and Interpreting the Spatial Electrical Fields of the Heart.
   JULIEN H. ISAACS, M.D., F.A.C.C., and J. LOUIS FREIBRUN, M.D., Los Angeles
   Department of Cardiology, University of California School of Medicine

3. Detection of Pulmonic and Tricuspid Valvular Regurgitation with an Indicator-Dilution Technic.
   N. PERRYMAN COLLINS, M.D., EUGENE BRAUNWALD, M.D., and ANDREW G. MORROW, M.D., Bethesda, Md.
   Clinic of Surgery, National Heart Institute

4. Heart Disease, Exercise and Cardiac Output.
   SYLVAN L. WEINBERG, M.D., F.A.C.C., G. RICHARD GROVE, PH.D., and ROBERT E. ZIPF, M.D., Dayton, Ohio
   Department of Research, Miami Valley Hospital

5. Clinical Observations on a New Coronary Vasodilator (Win 5494).
   RAYMOND HARRIS, M.D., F.A.C.C., Albany, New York
   St. Peter's Hospital

10:30–11:00 a.m.—Intermission

Chairman: GEORGE R. MENEELY, M.D., F.A.C.C., Nashville, Tenn.
Associate Professor of Medicine, Vanderbilt University School of Medicine

6. Impending Myocardial Infarction—Recognition and Management.
   R. E. BEAMISH, M.D., F.A.C.C., and V. MARIE STORRIE, M.D., Winnipeg, Canada
   Department of Cardiology, Manitoba Clinic

7. Valvular Replacement in Acquired Heart Disease.
   EARLE B. KAY, M.D., LOUIS HEAD, M.D., and CID NOGUEIRA, M.D., Cleveland, Ohio
   St. Vincent's Charity Hospital

8. Intravenous Injection of Hyaluronidase in Acute Myocardial Infarction: Preliminary Report of Clinical and Experimental Observations.
   HENRY A. ZIMMERMAN, M.D., F.A.C.C., and JORGE MARTINS DE OLIVEIRA, M.D., Cleveland, Ohio
   Cardiovascular Research Laboratory, Cleveland City Hospital

9. The Problem of Cerebral Angiospasm.
   ELIOT CORDAY, M.D., F.A.C.C., and SANFORD ROTHENBERG, M.D., Los Angeles
   Cardiac Clinic and Department of Neurosurgery, Cedars of Lebanon Hospital

Fourth Scientific Session

Wednesday, May 27, 1:30–3:30 p.m.

Symposium on

NEW ADVANCES IN THE RADIOLOGIC DIAGNOSIS OF HEART DISEASE

Moderator: ROBERT P. GLOVER, M.D., F.A.C.C., Philadelphia, Pa.
Director, Thoracic and Cardiovascular Surgery and Research, Presbyterian Hospital; Assistant Professor of Clinical Surgery, University of Pennsylvania School of Medicine

1. Image Intensification in Relation to the Diagnosis of Congenital Heart Disease.
   JOHN A. KIRKPATRICK, JR., M.D., Philadelphia
   Chief of Radiology, St. Christopher's Hospital for Children
2. The Use of Gas and Opaque Contrast Media in the Radiologic Diagnosis of Heart and Pericardial Lesions.
   HERBERT M. STAUFFER, M.D., Philadelphia
   Professor and Chairman, Department of Radiology, Temple University School of Medicine
3. Direct Intracardiac and Great Vessel Opacification Studies.
   J. STAUFFER LEHMAN, M.D., Philadelphia
   Professor and Chairman, Department of Radiology, Hahnemann Medical College and Hospital
4. The Experimental Roentgenologic Visualization of Normal and Abnormal Coronary Arteries.
   WILLIAM H. SEWELL, M.D., WADE H. SHUFORD, M.D., and PABLO A. DAVALOS, M.D., Atlanta, Ga.
   Division of Thoracic Surgery of the Department of Surgery, and Department of Radiology, Emory University School of Medicine and Grady Memorial Hospital

3:30–4:00 p.m.—Intermission

Annual Business Meeting

Wednesday, May 27, 4:00–5:30 p.m.

Groedel Memorial Lecture on Humanities in Medicine

Wednesday evening, May 27

The History of Coronary Disease.
PAUL KLEMPERER, M.D., New York
Consulting Pathologist, Mt. Sinai Hospital

Fifth Scientific Session

Thursday, May 28, 1959, 9:00 a.m.—Noon

Symposium on

THE USE AND ABUSE OF CARDIAC BYPASS

Moderator: J. MAXWELL CHAMBERLAIN, M.D., F.A.C.C., New York
Assistant Professor of Clinical Surgery, Columbia University Medical College; Director of Thoracic Surgery, Roosevelt Hospital

IVAN D. BARONOFSKY, M.D., New York
Director of Surgery, Mount Sinai Hospital; Clinical Professor of Surgery, Columbia University

DANIEL F. DOWNING, M.D., F.A.C.C., Philadelphia
Associate Professor of Pediatrics, Hahnemann Medical College

DONALD B. EFFLER, M.D., Cleveland
Professor of Thoracic Surgery, Frank E. Bunts Institute

10:00–10:30 a.m.—Intermission

CONRAD R. LAM, M.D., Detroit
Attending, Charge Thoracic Surgery, Henry Ford Hospital

HENRY SWAN, M.D., Denver
Professor of Surgery, University of Colorado

Sixth Scientific Session

Thursday, May 28, 2:00–5:30 p.m.

CONVENTION GUEST LECTURE

Thursday, May 28, 2:00–3:00 p.m.

Introduction: JOHN S. LADUE, M.D., F.A.C.C., New York
Associate Professor of Clinical Medicine, Cornell University Medical College, Section Head Cardiology, Memorial Center for Cancer and Allied Diseases

The Role of Blood Coagulation and Fibrinolysis in Arteriosclerosis.
TAGE ASTRUP, M.D., Copenhagen
Carlsbergfondets Biologiske Institut

3:00–3:30 p.m.—Intermission

Symposium on

MANAGEMENT OF COMPLICATIONS ATTENDANT TO CARDIAC SURGERY

Moderator: OSLER A. ABBOTT, M.D., F.A.C.C., Atlanta
Associate Professor, Chief, Division Thoracic and Cardiovascular Surgery, Emory University School of Medicine

1. Influence of Preoperative Management.
   R. BRUCE LOGUE, M.D., Atlanta, Ga.
   Professor of Medicine, Chief Division of Cardiology, Emory University School of Medicine

2. Complications Attendant to Anesthesia.
   KENNETH K. KEOWN, M.D., Columbia, Mo.
   Professor and Chairman, Department of Anesthesia, University of Missouri School of Medicine

3. Complications Attendant to Closed Cardiac Surgery.
   OSLER A. ABBOTT, M.D., F.A.C.C., Atlanta
   Associate Professor, Chief Division Thoracic and Cardiovascular Surgery, Emory University School of Medicine

4. Complications Attendant to Open Cardiac Surgery.
   C. WALTON LILLEHEI, M.D., F.A.C.C., Minneapolis, Minn.
   Professor of Surgery, University of Minnesota Medical School

Seventh Scientific Session

Friday, May 29, 9:00 a.m.–12:30 p.m.

A. *Symposium on*

SOME RECENT ADVANCES IN CLINICAL AUSCULTATION OF THE HEART

Moderator: W. PROCTOR HARVEY, M.D., Washington, D. C.
Professor and Head, Department of Medicine, Georgetown University Medical Center

JACK P. SEGAL, M.D., JOSEPH K. PERLOFF, M.D., MICHAEL A. CORRADO, M.D., RECEP ARI, M.D., FRANK MARCUS, M.D., BERNARD SEGAL, M.D., CHARLES FRAHM, M.D., MAURICE A. CAPONE, M.D., and MAURICE AYGEN, M.D., Washington, D. C.
Department of Medicine, Division of Cardiology, Georgetown University Hospital

10:30–11:00 a.m.—Intermission

B. *Symposium on*

PHONOCARDIOGRAPHY AND CHEST WALL VIBRATIONS

Moderator: ALDO A. LUISADA, M.D., F.A.C.C., Chicago
Associate Professor of Medicine and Director, Division of Cardiology, Chicago Medical School, and Mount Sinai Hospital

1. Objective Proof of Functional Rumbles Simulating Mitral Stenosis (Autopsy, Right and Left Heart Catheterization).
   ALDO A. LUISADA, M.D., F.A.C.C.

2. Studies of Ultra-Low Frequency Precordial Movements (Kinetocardiograms).
   E. E. EDDLEMAN, JR., M.D., Birmingham, Ala.
   Associate Professor of Medicine, Medical College of Alabama

3. Low Frequency Tracings of Precordial Displacement and Acceleration.
   LESLIE M. ROSA, M.D., Chicago
   Division of Cardiology, Chicago Medical School

Eighth Scientific Session

Friday, May 29, 2:00–3:30 p.m.

Symposium on

PRESENT AND FUTURE OF CINEANGIOCARDIOGRAPHY

Moderator: ISRAEL STEINBERG, M.D., New York
Associate Professor of Clinical Radiology, Columbia University Medical School

Introduction: The Normal Heart.
ISRAEL STEINBERG, M.D.

1. Acyanotic Congenital Heart Disease.
   JOHN A. CAMPBELL, M.D., Indianapolis
   Chairman and Professor of Radiology, Indiana University School of Medicine

2. Cyanotic Congenital Heart Disease.
   J. GERARD MUDD, M.D., St. Louis
   Assistant Professor of Medicine, St. Louis University School of Medicine

3. Biplane Cineangiocardiography with 11-Inch Image Intensifiers.
   HERBERT L. ABRAMS, M.D., San Francisco
   Associate Professor of Radiology, Stanford University School of Medicine

4. Acquired Heart Disease.
   F. MASON SONES, JR., M.D., Cleveland
   Director of Cardiac Laboratory, Cleveland Clinic Foundation

Local Arrangements Committee

ROBERT P. GLOVER *and* FRANKLIN C. MASSEY, *Co-Chairmen*

JOSEPH B. CADY
ANTHONY D. DALE
JULIO C. DAVILA
JAMES B. DONALDSON
DANIEL F. DOWNING
MARY H. EASBY
DAVID GELFAND
JESSE G. HAFER
O. HENRY JANTON
J. RODERICK KITCHELL
MICHAEL MARGOLIES
THOMAS J. E. O'NEILL
JAMES E. PUGH
ROBERT G. TROUT
JOHN R. VASTINE
GEORGE R. VILSACK
MRS. ROBERT P. GLOVER
MR. JOSEPH P. SUNNAR

Convention Activities

Annual Business Meeting

The Annual Business Meeting for the transaction of necessary College business will be held promptly at 4:00 P.M. on Wednesday, May 27, in the Crystal Ball Room. All Fellows are urged to attend and take part in the administrative affairs of the College. Included in the order of business will be the following:

1. Welcoming address by the President, DR. GEORGE W. CALVER.
2. Annual report of the Secretary and Treasurer.
3. Vote on Constitutional Amendments.
4. Election of new officers and trustees for 1959–60.
5. Installations of DR. OSLER A. ABBOTT as the new President of the College.

Convocation

The Annual Convocation of the College will take place Wednesday at 8:30 P.M. Certificates of Fellowship will be conferred on candidates. Dress will be black tie. Candidates will assemble with the Marshal at 8:30 P.M. and the Processional will begin at 8:45 P.M. The Convocation will take place in the Crystal Ball Room.

At this Convocation certificates of Honorary Fellowship will be conferred on Paul Wood, O.B.E., M.D., F.R.C.P., London, England, Francis L. Chamberlain, M.D., D.SC., San Francisco, Calif., and Irvine H. Page, M.D., Cleveland, Ohio.

The Convocation will close with the Groedel Memorial Lecture by Dr. Paul Klemperer of New York, N. Y., and the conferring upon Dr. Klemperer of the Groedel Medal for 1959.

All newly elected Fellows are urged to attend the Convocation. They are reminded that Certificates will not be conferred in absentia. The Convocation Register must be signed by noon of the Convocation Day.

Reception, Annual Banquet, and Dance

Reception and cocktail hour will start at 6:00 Thursday evening in the Crystal Ball Room. The Annual Banquet will start at 7:00 and will run until 9:00; there will be no serious speeches; President Calver will introduce the honored guests of the College.

From 9:00–10:00 a professional entertainment group will be presented. After the entertainment there will be dancing until midnight.

Tickets for this event will be available at the Registration Desk.

For the reception and cocktail hour the College is again indebted to Joseph E. Seagram & Sons, Inc.

Film Program

Medical motion pictures will be shown in the Crystal Ball Room Lounge from 12 noon to 2 P.M. daily.

A corrected list showing exact time of showing on each day's schedule will be available at the Registration Desk during the Convention.

Tuesday

1. Physiology of Anoxia. U. S. Naval Medical Center, Pensacola, Fla.
2. Physiology of High Altitude Flying. U. S. Naval Medical Center, Pensacola, Fla.
3. Congenital Malformations of the Heart (Part I: Development of the Normal Heart). ROBERT F. RUSHMER and RICHARD J. BLANDAU
4. Congenital Malformations of the Heart (Part II: Acyanotic Congenital Heart Disease). ROBERT F. RUSHMER
5. Congenital Malformations of the Heart (Part III: Cyanotic Congenital Heart Disease). ROBERT F. RUSHMER

Wednesday

6. The Application of Cinefluorography to the Study of Congenital Heart Disease. HARRY M. WOSKE
7. Visualization of Intracardiac Structure by Intravascular Injection of Carbon Dioxide. T. M. DURANT, H. STAUFFER, and M. J. OPPENHEIMER
8. Left and Right Heart Catheterization. ALDO A. LUISADA
9. Cardiac Catheterization and Angiocardiography in Infants. I. B. BOESEN, Copenhagen

Thursday

10. Extremely Light Analgesia Plus Muscle Relaxation for Major Cardiac Surgery. SEYMOUR SCHOTZ
11. Closure of Ventricular Septal Defects. JOHN Y. TEMPLETON, 3rd

12. Closure of Interventricular Septal Defects Using Extra Corporeal Circulation and Elective Cardiac Arrest. G. P. Rosemond, R. R. Tyson, and W. C. Wright
13. The Mitral Valve—Dynamic Pathology and Surgery. Robert P. Glover
14. Aneurysms of the Abdominal Aorta: Surgical Considerations Based Upon Analysis of 500 Resected Cases. Michael E. De Bakey, Denton A. Cooley, and E. Stanley Crawford

Friday

15. Surgical Treatment of Aneurysm. Michael E. De Bakey, Denton A. Cooley, *et al.*
16. Cardiac Arrest. Henry Swan (1958)
17. Surgical Considerations in the Treatment of Cerebral Arterial Insufficiency. E. Stanley Crawford, Michael E. De Bakey, and George C. Morris
18. Congestive Heart Failure. Dwinnell Grant
19. Normal Fluoroscopy of the Chest. Paul K. Bornstein and Irving J. Selikoff

Reserve films (shown on request):

20. Post Operative Aerosol Therapy. Max S. Sandove and Ruben C. Balagot
21. Surgical Management of Coronary Heart Disease. M. S. Mazel
22. Peripheral Circulation: Plethysmographic Observations. Travis Winsor
23. Procedures in the Diagnosis of Cardiovascular Disease. University of Southern California
24. The Recognition and Management of Respiratory Acidosis. R. H. Smart, H. L. Motley, and J. F. Boyle
25. The Anatomic Basis of Surgery of Mitral Insufficiency. Robert P. Glover

Special Exhibit

"Working Together to Keep Hearts Strong, 1948–59." National Health Institute, Bethesda, and American Heart Association, New York

Scientific Exhibits

Prevention of Streptococcal Infection in Rheumatic Fever. Summary of a Four-Year Study. Benedict F. Massell, M.D., Teogenes A. Carbonilla, Shekhar Jhaveri, M.D., Raphael B. Reider, M.D., House of the Good Samaritan, Boston, Mass.

Heparin and the Removal of Lipids from the Blood. Hyman Engelberg, M.D., Beverly Hills, Calif.

The Hemodynamic Concept of Atherosclerosis. Meyer Texon, M.D., New York University Post-Graduate Medical School and Office of the Chief Medical Examiner, City of New York

Surgery of Acquired and Congenital Heart Disease. Earle B. Kay, M.D., Cleveland, Ohio

Hypertension: Newer Aspects of Therapy and Effects upon Vascular Deterioration. John R. Beem, M.D., Nelson H. Schimmel, M.D., John H. Moyer, M.D., and Joseph Rosenfeld, M.D., Hahnemann Medical College and Hospital, Philadelphia

Blood of Man. William P. Murphy, Jr., M.D., American Association of Blood Banks, Miami

Shock and Arrhythmias: Their Management. Arthur Bernstein, M.D., Jerome W. Kaufman, M.D., Fred Cohen, M.D., Bernard Robins, M.D., Franklin Simon, M.D,, and Edwin Rothfeld, M.D., Newark Beth Israel Hospital, Newark, N. J.

Combined Medical Surgical Therapy in the Treatment of Coronary Heart Disease. M. S. Mazel, M.D., Edgewater Hospital, Chicago

Cardiac Surgery. Dwight E. Harken, M.D., Armand A. Lefemine, M.D., Warren J. Taylor, M.D., George Albertal, M.D., Peter Bent Brigham Hospital and the Laboratory for Surgical Research, Harvard Medical School, Boston

The Practical Diagnosis of Surgical Heart Disease. Robert P. Glover, M.D., The Presbyterian Hospital; Julio C. Davila, M.D., Thomas M. Fitzgerald, Mercy Hospital; Robert G. Trout, M.D., St. Christopher's Hospital for Children, Philadelphia

Spatial Vectorcardiography. Lewis Gunther, M.D., The College of Medical Evangelists and the Federal Aviation Agency, Los Angeles

Blue Dye Test for Mitral Insufficiency. George J. Magovern, M.D., Lawrence Brent, M.D., Donald L. Fisher, M.D., and Edward M. Kent, M.D., University of Pittsburgh School of Medicine, Pittsburgh

Transbronchial Left Heart Catheterization. Carl J. Impellitier, M.D., Rochester, N. Y.

Edema Mechanisms and Diuretic Therapy. John H. Moyer, M.D., John R. Beem, M.D., Tibor Bodi, M.D., Morton Fuchs, M.D., Joseph Rosenfeld, M.D., and Lewis Mills, M.D., Department of Medicine, Hahnemann Medical College and Hospital

Drug Therapy in Hypertension. Marvin Moser, M.D., and Alice I. Macaulay, M.D., White Plains, N. Y.

Drug Therapy in Angina Pectoris. Henry I. Russek, M.D., Staten Island, N. Y.

Heart Anatomy. O. V. Batson, M.D., Graduate School of Medicine, University of Pennsylvania, Philadelphia